American Heart Journal

An international publication for the study of the circulation

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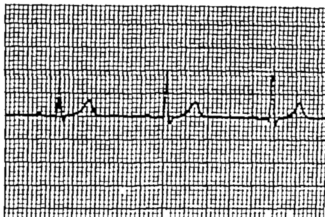
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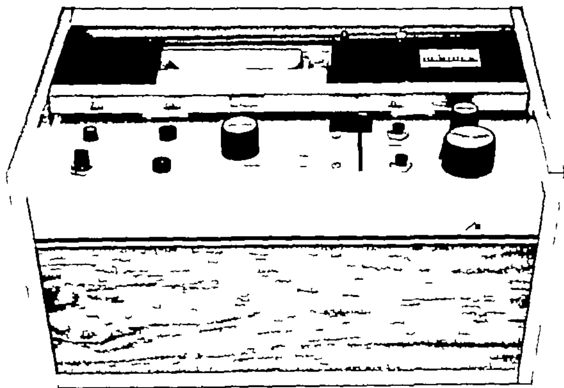
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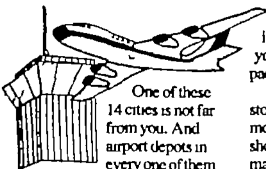
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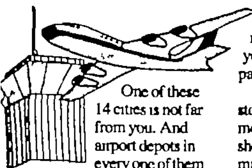
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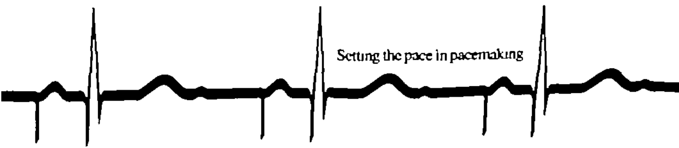
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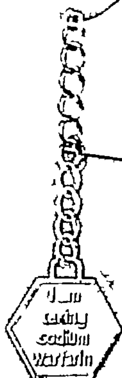
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the tag tells the story

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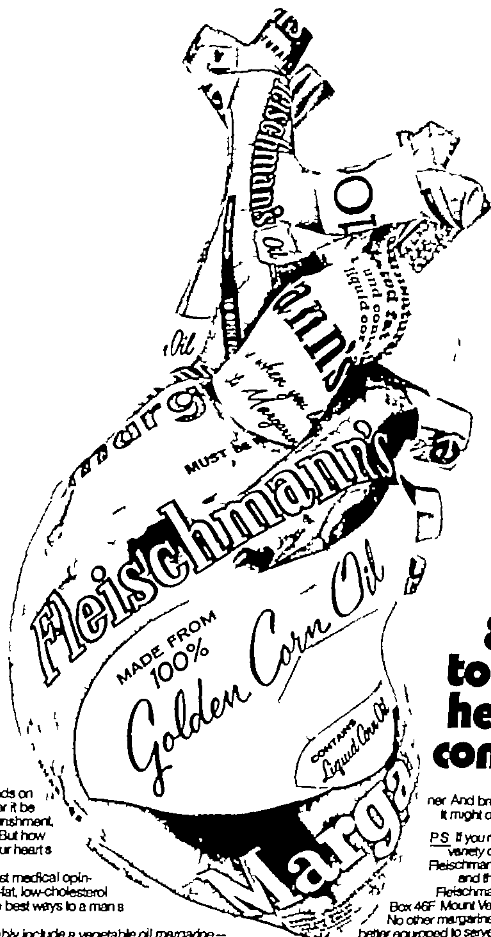
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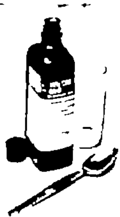
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Welt L. G. In Goodman L. A and Gilman, A. eds The Pharmacological Basis of Therapeutics ed 3 New York The MacMillan Co 1965, p 790

POTASSIUM... IN BALANCE OR IMBALANCE?

When optimum retention and utilization of potassium are essential Kay Ciel (potassium chloride) restores and maintains the electrolyte balance



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Contraindications: *Severe or progressive kidney disease or* dysfunction (possible exception: nephrosis). Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity to the drug. Continued use in developing hyperkalemia. Do not give potassium supplements, either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported. Check *BUN* and serum potassium periodically, especially in the elderly and those with suspected or confirmed renal insufficiency. Use *in pregnancy only when essential to* patient welfare.

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July 1971 Volume 82 Number 1

Editorial

The controversial role of magnesium in protein-calorie malnutrition

Eric U Rosen M.B Ch.B., M Med (Paed) D C.H
Johannesburg South Africa

Children with protein-calorie malnutrition (PCM) are prone to major electrolyte disturbances. The use of potassium in intravenous fluid replacement therapy dramatically improved the survival rate of patients with this condition Nevertheless, the mortality rate in cases of PCM is still 20 per cent. Other than potassium magnesium is the most abundant intracellular cation and consequently over the last ten years, its homeostasis in patients with nutritional deprivation has evoked great interest. The development of an accurate method of body fluid magnesium estimation gave further impetus to the investigation of possible states of magnesium deficiency

Evidence of magnesium depletion in PCM derived from analysis of muscle biopsy material,[1-4] estimations of urinary plasma and serum magnesium and magnesium balance studies[1,4] is well documented However the reported frequency of magnesium depletion in PCM has varied widely[4] and the exact clinical expression of this metabolic upset is as yet undetermined.

At present the practical assessment of magnesium depletion is based upon the measurement of urinary magnesium levels, which fall virtually to zero in the presence of magnesium deficiency as well as the plasma or serum magnesium. Although the latter does not accurately reflect the state of intracellular magnesium it still gives a good indication of total body magnesium depletion and remains the most convenient index by which the liability to symptoms from magnesium deficiency can be determined Plasma levels of less than 1.2 mg per 100 ml are indicative of substantial magnesium loss.[1]

Measurement of plasma and urinary magnesium is best carried out by atomic absorption spectrophotometry which gives very accurate results.[7] This is of great importance as the normal concentration of magnesium in the plasma is extremely low and only accurate estimations will show variations from the norm

Montgomery[7] and Back, Montgomery and Ward[8] reported the occurrence of tremors, twitching and convulsions in infants with low serum magnesium levels

From Baragwanath Hospital and the University of the Witwatersrand, Johannesburg, South Africa.
Received for publication Dec. 21, 1970.
Reprint requests to: Eric U Rosen, M.D Pediatric Department, Transvaal Provincial Hospitals, Baragwanath Hospital, Northcliff, Johannesburg, South Africa.

who had PCM they also discussed 2 patients with normocalcemic tetany which responded to magnesium therapy There also appears to be a complex link between the levels of calcium and magnesium in the blood which is as yet imperfectly understood [10] At present the neuroexcitatory effect of hypomagnesemia appears to be the only well-documented disturbance exhibited in patients with magnesium deficiency

In Nigeria Caddell and Goddard[3] showed that magnesium deficiency was common in children with PCM Caddell [11] herself then conducted a double blind paired sequential trial to assess the efficacy of parenteral magnesium therapy in this condition Her preliminary findings indicated that this form of therapy was of such significant value that the double blind trial was stopped before completion in order to give the control patients the benefit of therapy also The clinical symptoms she attributed to magnesium depletion included weakness anorexia tremors sleeplessness hyper irritability hypotension hypothermia and electrocardiographic changes (A V node or sinus tachycardia and flat or inverted T waves in the left precordial leads) all of which improved rapidly after magnesium administration Unfortunately no magnesium estimations were carried out on the patients in the double-blind trial and correlation of symptomatology with plasma magnesium levels could not be verified

Another trial of magnesium therapy was undertaken in South Africa[12] where, of 100 consecutive children with severe PCM requiring admission to the hospital 50 were randomly allocated to parenteral magnesium therapy while the other 50 acted as controls. All children had plasma magnesium estimations carried out within 24 hours of admission and repeatedly throughout their stay in the hospital Although initial plasma magnesium levels were commonly lower than normal and tended to fall transiently in untreated cases the trial failed to demonstrate any therapeutic benefit in the 50 treated children The over all mortality rate in both groups was 21 per cent and the rate of recovery with the use of the criteria suggested by Caddell [11] was the same in both groups. In no instance was it possible to recognize clinically the children who had the lowest plasma magnesium levels nor were there any specific symptoms identifiable with magnesium depletion Although tremors were observed in 11 children and convulsions in 5 in no instance could one relate them to hypomagnesemia. Electrocardiograms were obtained in 25 patients on admission but apart from sinus tachycardia they showed nothing of significance As many of the patients were pyrexial and had infections it is more likely that the tachycardia was attributable to this rather than to hypomagnesemia In only one child was there a possibility that demise could be attributed to magnesium depletion and then solely because it was the one biochemical abnormality demonstrated on the day of death

The possibility that parenteral magnesium sulfate is poorly or slowly absorbed in children with PCM of the kwashiorkor type in whom marked edema is the most prominent finding and who have sluggish circulations was investigated by Rosen and Moosa.[13] They showed that absorption of magnesium was rapid and that the plasma magnesium level rose significantly within 15 minutes of parenteral administration

The discrepancies in the results of the Nigerian and South African series are difficult to explain Possibly the South African children are less severely depleted of magnesium than are those described by Caddell their staple diet being maize which has a much higher magnesium content than does cassava the main substance of diet in Nigeria This regional variation in the findings in cases of PCM is common[4] but fails to explain why even the most severely affected patients with the lowest plasma magnesium levels in the series of Rosen and associates[12] did not show any significant response to therapy Further clinical trials are obviously necessary before the importance of routine magnesium therapy in PCM can be fully assessed

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Fig. 1 Lateral -ray view of the chest showing permanent pacemaker catheter in coronary si us.

germicidal soap 24 hours prior to the operation, and tincture of Merthiolate was used at operation to prep the operative area. Local anesthesia was obtained with lidocaine 0.5 per cent. The left cephalic vein as it coursed in the deltopectoral groove appeared to be the most useful site of catheter entry although either external or internal jugular veins or lateral thoracic veins could have been used if necessary The development of smaller caliber catheters allowed the use of small venous tributaries and facilitated selection of a suitable vein.

The catheter was advanced under fluoroscopic control into the right ventricle. Perforation of a thin-walled right ventricle was a potential risk particularly with the newer smaller diameter catheters. This could be avoided by pulling back the catheter if frequent ventricular premature contractions were encountered and by withdrawing the stiffening stylet 2 to 3 cm from the tip so that a relatively soft catheter tip engaged the right ventricular wall

The apex of the right ventricle appeared to be the most stable site for pacemaking Occasionally the catheter inadvertently fell into the coronary sinus. This could have been suspected by the more medial and cephalad course of the catheter by the rhythmic up and down motion of the positioned catheter and by the failure to reach the ventricular apex. Fig 1 shows a lateral radiographic view with the pacing catheter in the coronary sinus. Electrical

Clinical communications

Use of the permanent transvenous pacemaker in 168 consecutive patients

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John Gregory M D
William J Grace M D
Stanley Giannelli Jr M.D
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New York N Y

The ease and simplicity of the transvenous method of cardiac pacemaker implantation has extended the use of permanent pacemakers to many patients who would not have been considered for a thoracotomy With the use of only local anesthesia and superficial dissection transvenous cardiac pacemaking is available to virtually any patient almost without regard to clinical status The development of reliable, demand type pulse generators suggest the prophylactic use of this technique in patients whose electrocardiographic patterns are considered to predispose to asystole [1] While preliminary reports are encouraging long term studies of large groups of patients are necessary to establish the best techniques, the proper indications, and the natural history of permanent transvenous pacing

This report describes 181 permanent transvenous pacemaker implantations in 168 consecutive patients between April 1 1965 and March 31 1970 at the St. Vincent s Hospital and Medical Center Fifteen of these cases have been previously reported [2] During this period technical improvements have given us the opportunity to study both fixed rate and demand type pulse generators.

Clinical material

Methods

PATIENT SELECTION Two groups of patients were considered for permanent transvenous pacemakers all patients with complete heart block regardless of clinical state and patients with unexplained vertigo or syncope who had other types of bradyarrhythmias.

SURGICAL TECHNIQUE Permanent transvenous pacemakers were implanted in the cardiac catheterization laboratory with a cardiac surgeon and cardiologist in attendance Penicillin 600 000 U streptomycin 0 5 Gm and oxycillin 1 0 Gm were administered 24 hours prior to operation and for four days postoperatively to prevent infection Appropriate changes in antibiotic therapy were made in individuals with histories of drug sensitivity

The skin was carefully cleansed with

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stimulation from the coronary sinus usually produces atrial pacing with a pacemaker impulse followed by a P wave and QRS complex but occasionally direct ventricular stimulation may occur producing a pattern of epicardial pacing which may be easily mistaken for endocardial pacing

Positioning was facilitated by the systematic search for the area of lowest threshold in the right ventricle Repeated measurements were made with an external threshold tester* connected to the catheter by sterile lead wires A threshold of 0 6 ma appeared acceptable in most patients.

The pulse generator was placed in a subcutaneous pocket anterior to the pectoralis major muscle This pouch was drained with a suction catheter for 24 hours postoperatively Neither long term antibiotics nor anticoagulants were used and the patients were generally discharged about seven days after operation

HEMODYNAMIC STUDIES Cardiac output was determined in duplicate at three ventricular rates in 13 patients prior to insertion of the permanent pacemaker A bolus of indocyanine green dye was injected into the pulmonary artery and arterial blood continuously withdrawn by a Harvard infusion withdrawal pump† The output of a Gilford Photometer‡ was directly recorded by a Texas Instrument Rectiriter§ as a dilution curve which was analyzed by the Stewart Hamilton method

THRESHOLD MEASUREMENTS Threshold measurements were repeated during pulse generator replacement in 25 patients, 4 to 29 months after the initial implantation Readings were obtained after the unit had been exteriorized and disconnected Sterile external lead wires were connected to the external threshold tester previously described and thresholds were measured in milliamperes and volts

FOLLOW-UP All patients with permanent pacemakers were followed every 3 months in a special pacemaker evaluation center At each visit the daily pulse records were examined and inquiry was made regarding symptoms of vertigo fainting or palpitations An (ECG) was taken to document rate and rhythm In patients with a ventricular triggered pacemaker the demand circuit was temporarily defunctionalized with a magnet so that the pacemaker function at fixed rate pacing could be checked The pacemaker impulse was analyzed and photographed on a synchronized oscilloscope.* The data from the previous visit were compared to the current observations and any variation was noted All pulse generators were replaced with a new demand type unit 30 months after implantation

PATIENT MATERIAL. One hundred and eighty-one permanent transvenous pacemakers were implanted in 168 patients between April 1965 and March 31 1970 There were 119 men and 49 women The age and sex division of the group is shown in Table I

The types of arrhythmias treated with permanent pacing are shown in Table II Complete heart block was present in two-thirds of the cases

One hundred and sixteen of the 168 patients were paced with a temporary transvenous electrode prior to the implantation of a permanent pacemaker Questions of the presence of digitalis toxicity or acute myocardial infarction were resolved by prolonged periods of observation up to four weeks in some cases. Patients with symptomatic sinus bradycardia were given a trial of anticholinergic drugs. Drug treatment of chronic complete heart block has been unsatisfactory and we have abandoned it except as emergency therapy before electrical pacing can be started Only 10 patients in the group with complete heart block denied syncope or vertigo while only 3 patients in Group B gave no history of syncopal episodes or attacks of vertigo A pulse rate below 60 beats per minute was documented at least once in over 90 per cent of the entire group In only 3 patients was permanent complete heart block produced by a documented myocardial infarction Of the 33 patients showing right axis deviation and left bundle branch block all but 3 had syncopal episodes Transition to complete heart

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Table I *Age and sex division for pacemaker implantations*

Sex	Age (years)				
	Under 50	*51 to 60*	*61 to 70*	*71 to 80*	*Over 80*
Male	5	13	45	36	20
Female	2	3	12	22	10

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In the absence of pacing failure there has been no recurrence of Stokes-Adams attacks. Thirty two of the 33 patients that showed right axis deviation and left bundle branch block have had no further syncopal attacks. The last patient died suddenly at home two weeks following implantation of his demand pacemaker. An autopsy was not performed.

Complications

We have not encountered infections, erosions of the skin, or extrusions of either pulse generator or electrodes. Runaway pacemakers or interference with pacemaker functions by external stimuli have not occurred. Three patients were found to have fractured electrodes after pacing failure was noted. Two were unipolar at 26 and 28 months and one was bipolar at 13 months. These units were replaced in entirety.

The complications are charted in two categories in Table III: bipolar versus unipolar systems. The most common complication has been wire dislocation. The over-all incidence is 8 per cent, but we have seen none in our last 62 cases. Nine of the 13 occurred in the first 48 hours following implantation. Nine displaced electrodes were initially placed via the external jugular vein, three via the left cephalic, and one via the left lateral thoracic vein.

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Table III *Complications*

Bipolar	*Complication*	*Unipolar*
9	Displacement	4
12	Failure	8
1	Runaway	0
1	Exit block	4
1	Electrode fracture	2
0	Perforation	2
0	Infection	0
Totals 43 units 996 patient months 23 patient months per unit	Fixed rate	12 units 310 patient months 26 patient months per unit
	Demand	111 units 1 108 patient months 10 patient months per unit

tory pacing in every case Nine more patients 5 with bipolar units and 4 with unipolar units, were seen 1 to 14 months after implantation with unit failure secondary to a rise in pacing threshold to an unacceptable level—greater than 2 0 ma Their units were replaced in entirety One patient was unknowingly paced via a catheter in the coronary sinus Failure of pacing occurred 7 days after implantation because of rise in the threshold and the catheter was repositioned

We have employed a total of 43 bipolar units all but 5 are of the fixed rate type for a total of 996 patient months, or 23 patient months per unit Twelve fixed rate unipolar units have been used for a total of 310 patient months an average of 26 patient months per unit We have followed 111 unipolar demand units for a total of 1 108 patient months or 10 patient months per unit For the calculations patients who died in less than 12 months were removed from the series.

Following failure to achieve satisfactory pacing with the use of a transvenous system three patients were paced via a transthoracic epicardial system Two of these patients were early in the series and would not be so treated now The third patient received a transthoracic unit after three unsuccessful attempts to establish endocardial pacing the last leading to a cardiac perforation

Three patients with unipolar pacemakers have returned with twitching of the pectoral muscle with each pacemaker pulse caused by spontaneous turning of the pulse generator in the pouch pocket, leaving the contact plate against the muscle. Simple external version cured this minor but annoying complication in all three patients.

Deaths

The 38 deaths that occurred in the group are charted in Table IV One death was operative caused by cardiac perforation tamponade and massive cerebral infarction Three deaths occurred in patients with fixed rate pacemakers and competing rhythms pacemaker induced ventricular fibrillation was suspected to be the cause of death This mechanism could not be excluded in 2 additional patients. Thirty two deaths appeared to be unrelated to the pacemaker Autopsy examination was performed on 12 of the 38 Advanced coronary artery disease was found in 7 of these patients. We have observed that ?5 per cent of our patients in complete heart block have reverted to sinus rhythm at some time in the follow up period

Threshold measurements

Repeat threshold measurements have been made in 25 patients, 11 with bipolar systems and 14 with unipolar systems at the time of elective or emergency battery replacement 4 to 30 months after implantation Six patients with bipolar systems showed no rise in threshold while 8 others

showed a significant rise but still within the output range of the bipolar pulse generator In the 14 patients with unipolar systems the thresholds were unchanged in 5 and rose 1 to 3 times the implantation level in 9 Our average follow-up with unipolar demand units is 9 7 months the median, 10 months, and the longest, 26 months. There have been 8 primary battery failures in the unipolar units, fixed-rate or demand type the earliest at 15 months.

Cardiac output studies at varying cardiac rates were performed on 13 patients. These studies have been reported in detail elsewhere and are summarized in Fig 2. Mean cardiac output rose from an average of 3.24 to 4 3 L. per minute as the heart rate was raised to 70 to 80 beats per minute In one patient cardiac output was not increased. Myocardial oxygen consumption increased in all patients.

We have found that the ECG will detect late unit failures but will not predict them Tracings must be taken of both fixed-rate and demand modes in the case of ventricular triggered pacemakers. Fig 3 shows the ECG tracings of apparently satisfactory demand-pacemaker function but failure of pacing on a fixed-rate basis. Fig 4 shows serial observations of a pacemaker impulse on a synchronized oscilloscope. The decline in the voltage was interpreted as impending battery failure and the unit was replaced. Fig 5 shows the variation in voltage with respiration

Table IV Deaths from April 1 1963 to March 31 1970

Patient	Age at death	Cause of death	Months paced
M. M.	89	Tamponade	36 hr
J C.	75	? Fibrillation	1
M W	70	? Fibrillation	½
A. R.	91	? Fibrillation	1
C. V	80	? Fibrillation	2
M D	71	? Fibrillation	3
D G.	68	Myocardial infarct	1
J B	63	Myocardial infarct	6
A. S.	57	Myocardial infarct	6
C. B.	80	Myocardial infarct	6
A. L.	76	Myocardial infarct	6
J H	70	Myocardial infarct	13
R. B	85	Myocardial infarct	15
R. J	66	Myocardial infarct	33
I K.	85	Stroke	1
M B	72	Stroke	2
N T	72	Stroke	3
M D	75	Stroke	3
M L.	70	Stroke	43
C. D	80	Heart failure	13
J D	83	Heart failure	18
D N	79	Heart failure	18
A. M.	85	Heart failure	29
J D	76	Pneumonia	2
J M	73	Pneumonia	15
A. E.	83	Pneumonia	38
A. R.	87	Trauma	11
R. W	68	Cirrhosis	14
J B	83	Carcinoma	31
R. G.	60	Unexplained	1
A. D	71	Unexplained	3
R. D	90	Unexplained	4
J G.	76	Unexplained	5
C. P	87	Unexplained	1
A. S.	80	Unexplained	12
N S.	67	Unexplained	12
J B.	74	Unexplained	24
E. S.	82	Unexplained	24

Discussion

Stokes-Adams attacks with intermittent or complete heart block are the chief indication for permanent cardiac pacing accounting for two-thirds of our series. One-third of our patients had symptoms and bradyarrhythmia that were not alleviated by drug therapy The studies of Schloff and associates,[4] Lasser Haft, and Friedberg and Lenegre[6] have prompted us to use the combination of left axis deviation and right bundle branch block ("bilateral bundle branch block") as an indication for a permanent pacemaker

Convincing data are lacking regarding the risk of death or permanent neurologic sequelae from Stokes-Adams attacks. It may be as Siddons and Sowton[7] suggest, that patients referred for permanent pacing are a selected group with a better prognosis for the worst cases will have died from the biological insult of cardiac arrest. The risk and morbidity of permanent pacemaking have been so low in our hands that we believe it is indicated if there is any question of vertigo or syncope being Stokes-Adams attacks. We believe a single attack is sufficient indication for a permanent pacemaker

We believe that the choice of the vein for introduction of the endocardial catheter

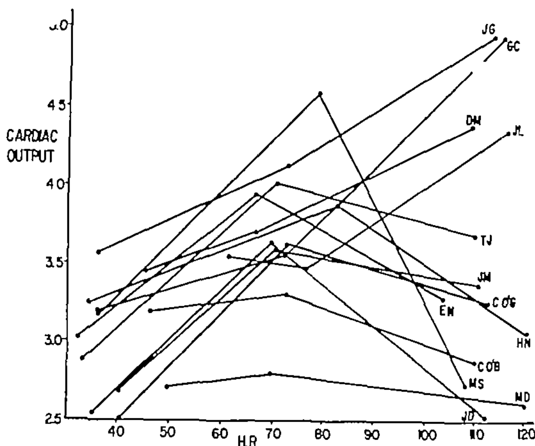


Fig. Cardiac output studies at varying heart rates in 13 patients.[14]

has little to do with the stability of the electrode tip in the right ventricle. In our experience, neither the left cephalic vein[9] nor the internal jugular vein[10] guarantees stability, although we prefer the cephalic vein for convenience, for then the entire procedure can be done through a single incision. Positioning the tip of the electrode catheter deep into the right ventricular apex and selection of the area of lowest pacing threshold will reduce to a minimum the incidence of dislocated catheters.[11] Our experience with coronary sinus pacing was inadvertent and unsatisfactory; it has been limited to the one case. Gonzales[12] reports two cases paced from this position with a 6 month follow-up, and the case described by Moss and associates[13] may be a third. Gabriele[14] suggests that it may be useful for temporary pacing. We agree with Siddons and Sowton,[7] who found that the threshold rises rapidly and that a stable position is difficult to achieve.

The pulse generator is usually placed in a subcutaneous pocket unless the skin and subcutaneous layers are particularly thin. While we have placed the pulse generator underneath the pectoralis major muscle in several patients, this position is not recommended because of the difficulty in changing pulse generators and the frequent occurrence of persistent shoulder pain.

We employ a demand type ventricle synchronized pacemaker in all cases.[15] One-quarter of our patients have been observed to revert back to sinus rhythm from complete heart block and hence have at least the potential to compete with a fixed rate pacemaker.

We believe that five sudden deaths early in the series and all with fixed rate pacemakers and competing rhythms may have been due to pacemaker induced ventricular fibrillation. Therefore, although the data of Furman, Escher, and Solomon[16] indicate that competing rhythms may not be dangerous, we believe that the demand type pacemaker is indicated in all patients. To date, although the follow-up period is short, we have found demand pacemakers as reliable as the fixed rate type,[17] failing to confirm the assumption that the more complex circuitry of the demand unit would be more prone to malfunction.[18]

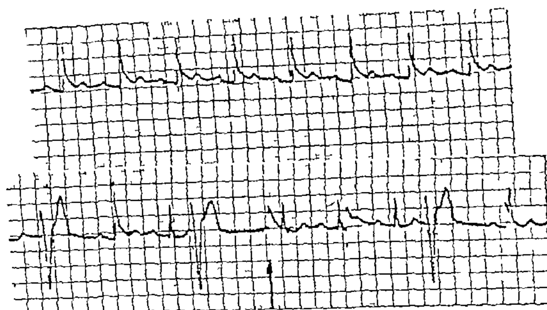


Fig. 3. *A*, ECG showing sinus rhythm with normal demand pacemaker impulse in QRS complex. This should not be taken as evidence of satisfactory pacemaker function. *B*, ECG from same patient as shown in *A* with demand circuit temporarily defunctionalized and pacemaker functioning as fixed-rate unit. Note competing rhythm and mixed pacemaker beat.

The optimal rate for artificial pacing has not been established. Cardiac output studies performed in patients with chronic heart block have shown that, in general, output is diminished at slow rates and increases with artificial pacing at faster rates. When ventricular function is impaired, stroke volume is limited so that augmentation of cardiac output is dependent upon increase in heart rate. As a rule, cardiac output increases significantly at rates in the range of 60 to 75 beats per minute. Further increases in heart rate are often, although not necessarily, associated with a fall in cardiac output.[4] However, the rate response curves are quite variable and unpredictable. Fig. 2 illustrates the variability among a group of patients studied at our laboratory.[15] Furthermore, in trying to predict the optimal pacing rate effects of increased heart rate on myocardial oxygen demands must be considered. These increased demands would ordinarily be met by increases in coronary blood flow. In patients with extensive coronary artery disease the coronary bed may be unable to meet increased demands by increasing blood flow and may resort to anaerobic mechanisms. This may explain the occasional development of heart failure in patients paced at "accepted rates. Most centers use units set at 70 to 72 beats per minute. Since we believe that cardiac output almost invariably increases adequately at rates over 60 beats per minute, we arbitrarily set our demand pacemakers to respond at this level. To date, all of our patients paced at rates of 60 beats per minute have responded clinically in such a manner as to indicate that cardiac output is adequate. We have not observed battery failure in any of these patients although the follow-up is still too short to allow a definite conclusion regarding a possible increase in battery life due to the reduction of the pacing rate from 70 to 60 beats per minute.

The most common complication of transvenous pacemaker implantation is wire dislocation. This usually occurs in the first 48 hours after implantation and is a simple matter to correct under local anesthesia. The 13 instances of dislocation in the bipolar group do not represent a true incidence, as most of these were early in our experience and occurred with a catheter model now abandoned. The incidence of dislocation is now less than four per cent with improved catheter electrodes and increasing familiarity with the method.

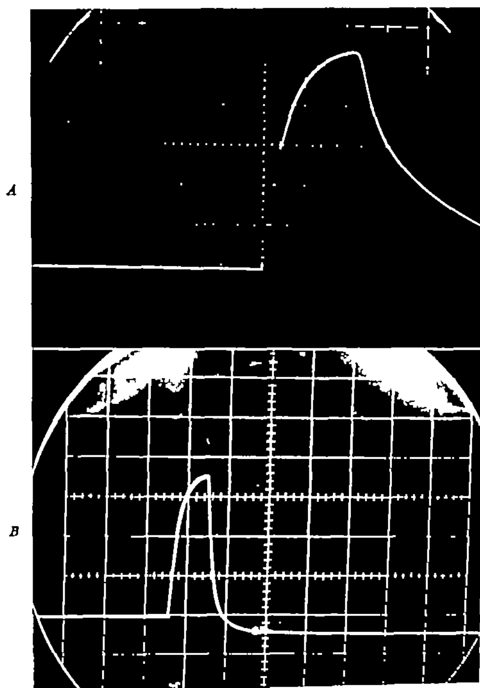


Fig 4 A Pacemaker impulse viewed on synchronized oscilloscope. Unipolar demand pacemaker immediately after implantation. B Repeat examination on same patient three mo ths after implantation. Note drop in voltage as measured by height of curve. Pacemaker pulse generator replaced.

With increasing experience with the transvenous method the indications for transthoracic epicardial pacing are in frequent. Although a recent series had but one death in 129 patients [11] Harthorne and associates[12] report 5 deaths (while pa tients were hospitalized) in 46 patients treated with transthoracic pacemakers and Gadboys Inkban and Litwak[13] re ported 46 complications in a series of 91 transthoracic implantations Harthorne and co-workers[12] have given up the trans-thoracic mode of implant after 18 electrode fractures in 44 patients who were followed for 12 months There are undoubtedly patients who cannot be satisfactorily paced by the transvenous method although in our experience such patients are rare.[1] Perforation per se is probably not an indication for thoracotomy [14] but if thora cotomy is necessary to deal with tam ponade, for example it seems reasonable to attach epicardial electrodes.

Permanent pacing in children poses a

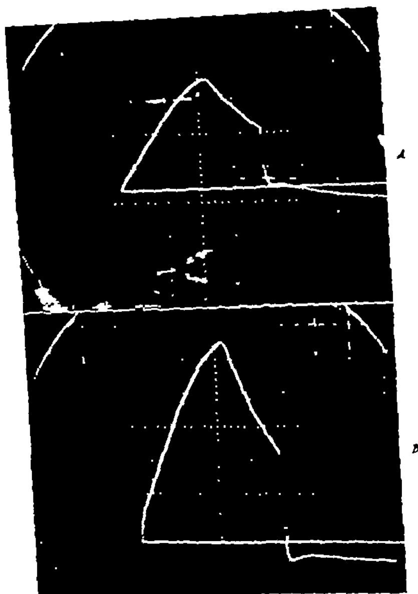


Fig. 5 *A* Photograph of the oscilloscopic trace of a bipolar pacemaker impulse taken during deep inspiration. *B* Photograph of the oscilloscopic trace of the same bipolar pacemaker impulse taken during deep expiration.

special problem Epicardial pacing with a demand-type pacemaker is probably the procedure of choice in this group. It has been assumed that long term transvenous pacing is not suitable in children because cardiac growth would tend to displace the catheter electrode.[14] This is yet to be proved. The long-term complications of epicardial pacing chiefly wire breakage and rising epicardial pacing threshold have run as high as 42 per cent in one series, and it is possible that the complications with the transvenous mode might prove to be lower than those with the epicardial method referred to above even in children Five of our patients had a late rise in pacing threshold or exit block which occurred with one type of bipolar catheter with a large tip It has now bee[n] discarded in favor of smaller models Forman and associates[15] have shown t[hat] the development of increasing thres[hold]

*Chardack-Greatbatch Model 5816, and Cordis Pa[...]

is a function of the surface area of the electrode tip That considerable individual variation exists is shown by our observation that only 50 per cent of our patients who have had repeat measurements show a significant rise in threshold The studies of Overdijk and Dekker[26] which indicate that a cathode intracardiac electrode may increase its threshold faster than an anode electrode may presage difficulty for unipolar cathode-endocardial systems. Only four of our patients with unipolar systems have had such difficulty up to two years after implantation Newer types of catheters such as the nonpolarizing electrode described by Parsonnet and associates[27] may solve this problem

Should late replacement of a complete transvenous unit be required removal of the old transvenous electrode may be impossible because of intracardiac or intravascular adhesions. We are currently following three patients with double sets of endocardial electrodes Possible complications could be catheter migration or perforation embolism or tricuspid insufficiency[28] So far none of these has been observed However nonfunctioning endocardial catheters should be removed if they can be easily dislodged

Implantation of a permanent pacemaker involves the physician in the responsibility for protection of the patient from the possible catastrophic effects of sudden unit failure The daily pulse record and serial ECG s are valuable in predicting impending battery failure but the most sensitive method appears to be the oscilloscopic analysis of the pacemaker impulse at repeated intervals a technique described by Knuckey McDonald and Sloman[29] and by Furman Escher and Solomon[16] Variation in pulse contour amplitude or decay too minute for detection otherwise can be measured by this method Such variation can mean impending unit failure Variation in the oscilloscope tracing of the pacemaker impulse can also be caused by respiration or positioning of the sensing electrodes. Our evaluation of this method of follow-up continues. At each follow up visit the ability of the pulse generator to pace satisfactorily as a fixed rate unit must be demonstrated for the ability of a ventricular triggered pacemaker to detect a QRS complex is insufficient evidence of satisfactory function With our current unipolar demand model* this is conveniently done with a magnet but the use of intravenous edrophonium chloride for this is described by Siddons and Sowton[7] With the use of these evaluations sudden unit failure is rare

Conclusions

1 Transvenous permanent endocardial pacemakers are safe effective and the procedure of choice in the treatment of Stokes-Adams attacks

2 Demand pacing systems are as reliable as the fixed rate units and are preferable in all patients

3 A wide variety of symptomatic bradyarrhythmias can be successfully treated with permanent transvenous pacemakers.

4 A pacemaker rate of 60 beats per minute is adequate for most patients.

Summary

One hundred and eighty-one implantations of permanent transvenous cardiac pacemakers have been performed in 168 patients at the St Vincent s Hospital New York N Y from April 1965 to March 1970 The chief indication for the implantations was complete heart block although one third of the patients were symptomatic from other bradyarrhythmias. Only ventricular triggered demand units have been used in the last two years. Cardiac output studies at varying rates indicated a rate of 60 beats per minute to be adequate in the group so studied and all pacemakers are set at this rate All patients have been relieved of symptoms. Complications have been minimal The demand type pacemaker has proved as reliable as the fixed rate unit and appears preferable in all patients.

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Atrial arrhythmias and lipomatous hypertrophy of the cardiac interatrial septum

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Increased accumulation of fat in the epicardium with advancing age has been demonstrated in a number of studies.[1-4] The interatrial septum shares this age-associated increase in fat deposit[5] and when reaching considerable size has been termed lipomatous hypertrophy of the interatrial septum (LHIS).[5-8] Such collections have usually been considered of little clinical significance,[6-12] although two patients have been described in whom unusual atrial arrhythmias have been observed.[13,14]

We present here the clinical features of ten patients with lipomatous hypertrophy of the interatrial septum. The anatomic details of this group have been described elsewhere.[8] Atrial arrhythmias, frequently of unusual types, were seen in all patients. In some patients an unusual "dome and dip" P wave configuration was noted in Leads II, III, and aV_F of the electrocardiogram. We suggest that these arrhythmias may be related to the excessive accumulation of fat in the interatrial septum and that the described P wave morphology may be an indicator of interatrial block due to such accumulation.

Methods

The recognition at autopsy of two cases of lipomatous hypertrophy of the interatrial septum prompted a search for additional cases. Review of autopsy files yielded five cases that usually had been indexed under lipoma of the heart. These cadavers were not available for direct examination, but microscopic sections of the interatrial septum were available from all and gross pictures were available from three. A personal review of approximately 1,000 consecutive autopsies by one of us (D. L. P.) produced another five cases in which direct gross and microscopic examination could be carried out. The local anatomy of the interatrial septum was studied in each case and general observations on the remainder of the heart were made. The clinical records of these ten patients were independently reviewed with particular study of all available electrocardiograms.

Results

In a study of 50 hearts collected at random,[8] the fat in the interatrial septum was always continuous with the epicardial

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fat and similar in amount (Fig 1) Fat was likely to be deposited in any available space in the interatrial septum sparing only the fossa ovalis and the sites of entrance of major vessels into the atrial chambers, particularly the coronary sinus. The largest accumulation of fat was usually anterior to the fossa ovalis and was bounded by the atrial walls on two sides, the fossa ovalis posteriorly the inter ventricular septum inferiorly and the epicardial surface superiorly and anteriorly

Details of the pathological findings in the ten cases of LHIS have been described elsewhere In these patients two general patterns of excessive interatrial septal fat were noted. The first consisted of an exaggeration of the usual wedge-shaped accumulation anterior to the fossa ovalis or a generalized increase in fat of uniform thickness throughout the septum The second pattern found in five cases, presented a greater bulging of the central portion of the anterior septum Histologic changes of myocardial atrophy and fibrosis in the interatrial septum were prominent in all cases of LHIS.

The pertinent clinical features are listed in Table I There were six women and four men all but one of whom were more than 70 years old. Three patients were notably obese, two were mildly obese, and five were of normal weight. At autopsy none of the patients had evidence of old or recent myocardial infarction Two had a few scattered foci of fibrosis in the left ventricle. Coronary sclerosis was absent in three patients, mild in five and moderate in two. Malignant tumors were found either before or after death in six patients two of the patients had double malignancies.

All of the patients had atrial arrhythmias. Eight had premature atrial beats which were frequent and often multifocal In addition three patients had multifocal atrial tachycardia[13] (Fig 2) three had wandering atrial pacemakers (Figs. 3 and 4) and two had paroxysmal atrial tachycardia Six patients had one or more of these latter three relatively unusual atrial arrhythmias. The seventh patient had manifestations of the sick-sinus syndrome including premature atrial beats sinus

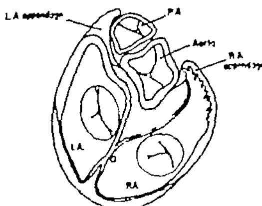


Fig 1 Drawing of a horizontal section of the heart made through the left and right atria (*LA* *RA*) at the level of the fossa ovalis (*FO*) looking down toward the atrioventricular valves. The stippled areas represent the usual pattern of fat deposition, the fat of the interatrial septum being continuous with the epicardial fat of the transverse pericardial sinus anteriorly behind the pulmonary artery (*PA*) and the aorta, and continuous with the epicardial fat of the posterior atrioventricular groove behind the fossa ovalis. (From Page, D L. Hum. Path. March, 1970, published by W B. Saunders Co.)

bradycardia, and episodes of sinus arrest The eighth patient had premature atrial beats alone. The remaining two patients had atrial fibrillation.

Leads II III and aVF on the electrocardiogram in one patient showed a P wave configuration that is very uncommon in these leads (Figs. 4 and 5) Similar but less striking examples of this P wave morphology were seen in the same leads of four other patients. Four of these five patients had the pattern of LHIS characterized by a more localized rounded bulging of the central portion of the anterior septum Conversely five patients had central bulging and four of these had this P wave configuration. This P wave has an initial broad dome-shaped positive deflection followed by a narrow deep negative deflection and thus has been called a dome and dip P wave Dome and dip is not to be confused with the term dome and dart used to characterize the P waves in Lead V_1 in some patients with left atrial rhythm[14] The dome and dip P wave was seen in what appeared to be normal sinus beats in some patients as well as in obviously ectopic atrial beats in others.

Table I Clinical and pathological features of patients with lipomatous hypertrophy of interatrial septum

Case	No. (Age and sex)	APB*	PAT*	MAT*	WAP*	Other	"Dome and dip P waves	Obesity	Cause of death	Weight of heart (Gm.) (Degree of coronary sclerosis)†	Myocardial scars‡	Malignant tumor
1R§	55693 (63F)	+				SB SA		−	70 per cent body burns	350 (+)	+	None
2R	1547653 (72M)	+			+		+	++	Pulmonary emboli chronic lung disease	310 (++)	−	Carcinoma of prostate
3	0872396 (73F)	+	+					++	Idiopathic pancytopenia uremia	450 (+)	−	Carcinoma of endometrium
4R	101350 (75M)	+		+	+	RBBB	+	++	Chronic pyelonephritis, uremia	740 (+)	+	None
5	610023 (77F)					AF		−	Myelogenous leukemia	3 0 (−)	−	Myelogenous leukemia meningioma
6R	799360 (77F)	+					+	−	Toxic hepatitis	410 (+)	−	Carcinoma of breast
7	0968621 (79F)	+		+		NPB VPB		−	Carcinoma of rectum	305 (−)	−	Carcinoma of rectum, carcinoma of ovary
8R	85 063 (81M)	+	+		+	NT* VPB RBBB	++	−	Chronic lung disease	490 (+++)	−	Carcinoma of lung
9	BH149041 (82F)					AF RBBB LAD*		+	Pulmonary infarct, CHF*	500 (+)	−	None
10	1551957 (83M)	+		+			+	+	Chronic lu g disease	520 (−)	−	None

APB, atrial premature beats; PAT paroxysmal atrial tachycardia; MAT multifocal atrial tachycardia; WAP wandering atrial pacemaker; SB, sinus bradycardia; SA, sinus arrest; RBBB right bundle branch block; AF atrial fibrillation; NPB, nodal premature beat; VPB, ventricular premature beat; NT nodal tachycardia; LAD, left axis deviation; CHF congestive heart failure.

†Absence of foci narrowing major coronary artery to less than 50 per cent of normal is considered negative. Foci of old or recent occlusion with narrowing to 10 per cent of normal luminal diameter would be considered 4+.

‡These represent few scattered small foci of fibrosis in the left ventricle. In no case was there an old or recent regional infarct.

§R indicates cases with rounded bulge of the central portion of the anterior septum. See text.

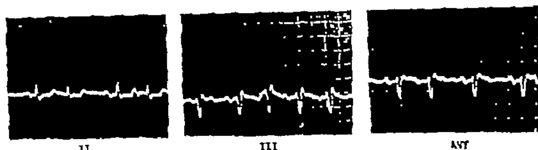


Fig. 2. Electrocardiographic Leads II, III and aVF in Case No. 4 showing multifocal atrial tachycardia.

Discussion

Seven cases of lipomatous hypertrophy of the interatrial septum have been reported in the literature.[4,13,14] Prior[4] described three women and two men ranging in age from 66 to 78 years old. The site of fat accumulation was anterior to the fossa ovalis in the three cases in which the site was designated. No electrocardiograms were shown and no mention was made of arrhythmias. The author concluded that the lipomatous changes represented variations in the normal structure of the interatrial septum. Kluge[13] described a 64-year-old man with a variety of refractory atrial arrhythmias including atrial fibrillation, premature atrial beats, wandering atrial pacemaker, and supraventricular tachycardia. LHIS found at autopsy was considered by the author to be the cause of the arrhythmias. Okel reported a case of type A Wolff-Parkinson-White syndrome in a 33-year-old person with fatal arrhythmias and autopsy findings of myocarditis, LHIS, and a prominent right moderator band. Atrial and later ventricular fibrillation were present. It was not clear which of the three pathological abnormalities may have been related to the arrhythmias.

Two cases similar to those described here have been reported as examples of cardiac lipomas. Five other cases probably are similar but insufficient information is available to indicate this with certainty. All seven cases were elderly patients with extensive poorly demarcated fat deposits anterior to the fossa ovalis. When mentioned, large amounts of epicardial fat were present. No clinical significance was attributed to these lesions.

In the present series all ten patients had atrial arrhythmias. Seven of the ten had unusual arrhythmias including multifocal atrial tachycardia, wandering atrial pacemaker, paroxysmal atrial tachycardia, and sinus arrest, all of which proved refractory to therapy. No common clinical factors could be found which might precipitate such arrhythmias. Postmortem examination including studies of the major atrial arteries revealed no evidence to indicate that coronary artery disease or generalized myocardial degeneration may have been predisposing factors. The only common pathological feature was an excessive accumulation of fat in the interatrial septum, suggesting that LHIS may be of functional significance related to the occurrence of these arrhythmias.

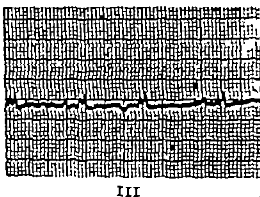


Fig. 3. Lead III in Case No. 2 showing a wandering atrial pacemaker.

The bizarre "dome and dip" configuration of the P waves in Leads II, III, and aVF of the electrocardiogram in one patient and the less striking occurrence of similar P-wave morphology in the same leads of four other patients may be an indicator of interatrial block related to this pathological phenomenon. It is of interest

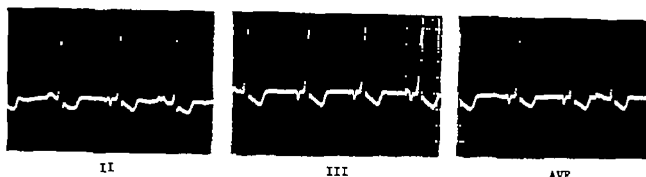


Fig 4 Leads II III and aVF of Case No. 8 showing a wandering atrial pacemaker The dome and dip configuration of the P waves is well seen in Lead III See text.

that the identifiable P waves in Lead aVF of a tracing in Kluge's case[13] showed a similar configuration Scherf and Cohen[17] presented the electrocardiogram of a 59 year-old man with an old inferior myocardial infarction in which P waves of similar morphology were present in Leads III and aVF They felt this was an example of interatrial block and that the best explanation assumed an activation of the right atrium beginning from the sinus node and proceeding inferiorly with later activation of the left atrium in an ascending direction

James[18] and more recently Merideth and Titus[19] have emphasized the existence of three pathways between the sinoatrial node and the atrioventricular node The larger anterior and middle pathways both course through the superior margins of the atrial septum and then pass inferiorly into the thick portion of the septum anterior to the fossa ovalis to connect with the atrioventricular node. Merideth and Titus[19] suggested that the prime functional significance of these pathways may be in the facilitation of orderly atrial depolarization the maintenance of sinus node control of ventricular depolarization under various physiological conditions, and the provision of orderly input into the atrioventricular node. Since the area anterior to the fossa ovalis is the most common site of fat accumulation in LHIS one might postulate that disruption of the anterior and middle internodal pathways may be the major etiologic factor in the production of the arrhythmias noted in these patients Passage of a depolarization wave down one or two pathways with terminal passage back up a partially interrupted pathway might

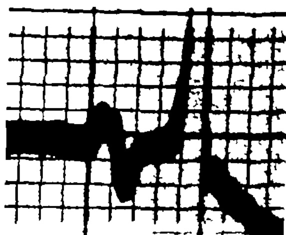


Fig 5 A magnification of the last P wave in Lead III of Fig 4 showing the 'dome and dip' morphology

explain the dome and dip configuration of the P waves in Leads II III and aVF of the electrocardiogram of some of these patients. The association of dome and dip P waves and the localized bulging pattern of LHIS in the anterior septum is consistent with this hypothesis.

The reason for the high incidence of malignant tumors in this series is not apparent. A significant factor may be a selection of patients living to an older age without long term heart disease resulting in a population more prone to the development of malignant growths

It appears that LHIS can occur independently of obesity or significant fatty infiltration of the ventricular myocardium Only three of our patients were obese and although increased epicardial fat was constant, significant fatty infiltration of the ventricular muscle was not seen[6]

The true incidence of LHIS is not known for in the common methods of postmortem cardiac dissection the interatrial septum is

not examined. Thus, the more usual pattern of fat deposition with uniform or tapering separation of the atrial walls without localized bulges, would not be expected to arouse the interest of the examiner because the atrial wall contour is not abnormal. It is only when the interatrial wall is cut that the striking finding is evident. It is hoped that future studies including routine cutting of the atrial septum and examination of the interatrial conduction system especially in older patients with atrial arrhythmias or "dome and dip" P waves, will more clearly delineate the functional significance of lipomatous hypertrophy of the interatrial septum suggested by the present series.

Summary

Excessive accumulation of fat in the interatrial septum termed lipomatous hypertrophy of the interatrial septum was found at postmortem examination in ten elderly patients. All patients had atrial arrhythmias. Seven patients had unusual arrhythmias including multifocal atrial tachycardia, wandering atrial pacemaker, paroxysmal atrial tachycardia, and sinus arrest, all of which proved refractory to therapy. In five patients an unusual "dome and dip" P wave configuration was noted in Leads II, III, and aV_F of the electrocardiogram. It is suggested that these arrhythmias may be related to the excessive accumulation of fat in the interatrial septum and that the described P wave morphology may be an indicator of interatrial block due to such accumulation.

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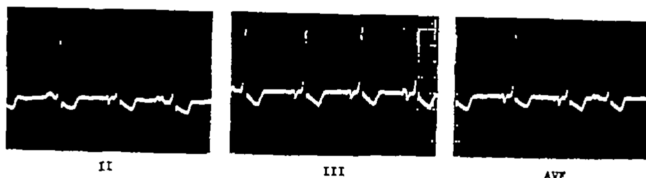


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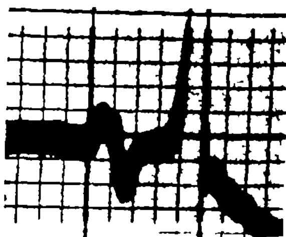


Fig. 5. A magnification of the last P wave in Lead III of Fig. 4 showing the "dome and dip" morphology.

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The true incidence of LHIS is not known, for in the common methods of postmortem cardiac dissection the interatrial septum is

bar spinal segments inclusive, total sympathetic denervation results when local anesthetic is injected into the midlumbar subarachnoid space and allowed to ascend in the subarachnoid space until concentrations adequate to block nerve transmission are achieved in high thoracic or low cervical sensory dermatomes. The concentration of spinal anesthetic agent in cerebrospinal fluid decreases as a function of distance from the site of injection.[11] When combined with the fact that the sensitivity of nerve fibers to the effects of local anesthetics is inversely related to nerve fiber size, the result is the presence of segmental zones of differential blockade at cephalad levels of spinal anesthesia.[11] Since preganglionic sympathetic fibers are smaller than somatic afferent fibers, which in turn are smaller than somatic motor fibers, sympathetic denervation extends an average of two spinal segments more cephalad than the area made anesthetic to pinprick.[11] Similarly the level of sensory anesthesia extends an average of two segments beyond the level of somatic motor blockade.[11] Total sympathetic denervation is, therefore, achieved when sensory levels of anesthesia extend to the second or third thoracic dermatomes, yet because somatic motor blockade is at the fourth or fifth thoracic level the muscles of respiration are unaffected to the extent that normal arterial oxygen and carbon dioxide tensions are maintained while the subject is spontaneously breathing room air.[11]

Patients were selected for the present study who were scheduled for lower abdominal or lower extremity elective surgery under spinal anesthesia. All were between the ages of 18 and 40 and were free of concurrent pulmonary and cardiovascular disease. Changes in heart rate were recorded subsequent to acute elevation of arterial pressure under two conditions: (1) during total *sympathetic* denervation with unimpaired vagal function (four subjects) and (2) during total sympathetic denervation combined with vagal blockade (two subjects). Acute elevations of arterial pressure were induced by producing peripheral vasoconstriction by the intravenous injection of the alpha-adrenergic stimulator methoxamine.[11]

Patients in the former group were premedicated with pentobarbital (150 mg. per 70 Kg. of body weight) intramuscularly 45 minutes before being placed in the supine position on an operating table in a quiet isolated room. Preoperative atropine was avoided. An intravenous infusion of 5 per cent dextrose in water was started and adjusted to run at a constant rate of 100 ml. per hour. Blood pressure was measured by sphygmomanometry and heart rate by palpation every two minutes until a steady state had been achieved as determined by absence of change greater than five per cent for 15 minutes or longer. The patient was then placed in the 10° head-down lateral position and hyperbaric tetracaine dextrose spinal anesthesia was induced with amounts of local anesthetic adequate to assure the desired high sensory levels of anesthesia. Epinephrine (0.3 to 0.4 mg.) was added to the intrathecal tetracaine dextrose solution to assure three hours of anesthesia. This amount of intrathecal epinephrine has no systemic effect.[11] After a second steady state of blood pressure and heart rate had been reached for at least 15 minutes following induction of spinal anesthesia (usually 40 to 50 minutes after injection of drugs into the subarachnoid space) methoxamine (0.07 mg. per kilogram) was rapidly injected intravenously and blood pressure and heart rate recorded for another 15 minutes. The operation may or may not have commenced at the time methoxamine was injected. Whether it had or not did not affect pressure or heart rate in the presence of complete sensory blockade.

Subjects studied during vagal blockade were managed in the same manner except that they received atropine (0.5 mg. per 70 Kg.) as additional premedication and after a steady state had been achieved following induction of spinal anesthesia, they received further atropine (0.04 mg. per kilogram) intravenously injected within 90 seconds. This dose of atropine has been shown safely to produce vagal blockade for at least 20 minutes.[14] Ten minutes after atropine administration, methoxamine (0.07 mg. per kilogram) was injected intravenously.

Mean arterial blood pressure (MABP)

Vagal component of the *chronotropic* response to baroreceptor stimulation in man

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Acute increases in arterial pressure are normally associated with reflex slowing of the heart rate The afferent arc of this reflex includes impulses arising from baroreceptors in carotid sinus and aortic arch areas. The efferent arc is less well defined There are three possibilities. The bradycardia could result from an increase in parasympathetic activity [1] inhibition of sympathetic activity [2,3] or simultaneous reciprocal changes in both sympathetic and parasympathetic activities [4-6] The difficulties in interpretation of experimental findings in terms of normal physiologic responses in man to elevation of arterial pressure are compounded by the fact that the majority of experimental data have been obtained from anesthetized animals Those studies which have been performed in man have relied upon pharmacologic blocking agents to inhibit one or the other portion of the autonomic innervation of the cardiac pacemakers and so have limitations inherent in the fact that autonomic blocking agents may have chronotropic properties independent of their effects on autonomic function [7,8]

We have evaluated the neural components in the efferent arc of the baroreceptor reflex in normal man by measuring pulse rate responses to pharmacologically induced acute elevations of arterial pressure in the presence of complete sympathetic denervation and in the presence of sympathetic denervation combined with parasympathetic blockade We have relied upon spinal anesthesia as a technique for producing pure sympathetic denervation[9] free of pharmacologic and chronotropic side effects associated with sympathetic ganglionic blocking agents and inhibitors of adrenergic receptors By superimposing parasympathetic blockade with atropine upon preexisting sympathetic denervation we have avoided the problems associated with the fact that in large doses atropine also affects sympathetic ganglionic transmission [10]

Methods

Spinal anesthesia produces preganglionic sympathetic denervation in the subarachnoid space. The amount of local anesthetic used is so minimal it has no systemic effects following vascular absorption [11] Since preganglionic sympathetic fibers in man arise from the first thoracic to the second lum

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Table I Mean arterial pressure and heart rate before spinal anesthesia after spinal anesthesia but before methoxamine and after methoxamine combined with spinal anesthesia (average readings for 15 minutes)

Patient	Before spinal		After spinal before methoxamine		After methoxamine			
					MABP		HR	
	MABP (mm Hg)	HR (beats/min.)	MABP (mm Hg)	HR (beats/min.)	mm. Hg	Change* (%)	Beats/min	Change* (%)
1	73	97	48	78	61	+27	60	−23
2	75	68	67	64	73	+ 9	45	−42
3	87	72	57	60	64	+12	40	−33
4	74	93	58	85	78	+34	78	− 8
Average change						+20 5		−26 5

*Percentile change from premethoxamine values.

Table II Mean arterial pressure and heart rate before spinal anesthesia after spinal anesthesia but before atropine after atropine and after atropine plus methoxamine

Patient	Before spinal*		After spinal before atropine*		After atropine†		After methoxamine†			
							MABP		HR	
	MABP (mm Hg)	HR (beats/min.)	MABP (mm Hg)	HR (beats/min.)	MABP (mm Hg)	HR (beats/min.)	Mm. Hg	Change‡ (%)	Mm Hg	Change‡ (%)
5	104	98	96	84	85	96	129	+52	101	+ 5
6	90	69	68	60	89	96	140	+57	113	+17

*Average reading for 5 minutes.
†Average reading for 8 minutes.
‡Percentile change from premethoxamine levels.

methoxamine bradycardia. The present investigation emphasizes that atropinization eliminates and indeed reverses the bradycardia induced by methoxamine in the presence of total sympathetic block.

Other studies[8,16] on the effect of the sympathetic denervation of spinal anesthesia on the chronotropic response to methoxamine have led to the conclusion that the slowing of heart rate induced by methoxamine is not reflexly mediated This conclusion can however be questioned on the basis that in the subjects studied sympathetic denervation was less than complete and on the basis that methoxamine was not administered during combined autonomic denervation

The relatively modest levels of arterial hypotension observed during total sympathetic block in the present subjects may appear unusual In fact, arterial pressure routinely decreases but little in normal individuals during spinal anesthesia when they are maintained in the slightly head down position to assure maintenance of adequate cardiac output.[11] The range of changes in blood pressure and heart rate following sympathetic denervation in the present subjects reflects individual differences in response to sympathetic denerva

was calculated in millimeters of mercury with the use of the formula

$$MABP = \frac{(\text{systolic pressure}) + 2\ (\text{diastolic pressure})}{3}$$

Results

Complete sympathetic denervation was evidenced in all subjects by development of bilateral Horner's syndrome with warm dry vasodilated upper extremities. Sensory levels of anesthesia to pinprick ranged from the second thoracic to the seventh cervical levels.

Arterial pressure and heart rate (HR) decreased during spinal anesthesia in all subjects (Tables I and II) and remained stable for at least 15 minutes prior to administration of methoxamine (Table I) or atropine (Table II). The injection of methoxamine without prior atropine produced an increase in pressure and a further decrease in heart rate in all subjects (Table I). The degree to which pressure rose and heart rate decreased following methoxamine varied, but in no instance did heart rate increase or pressure fail to rise. The increase in mean pressure averaged 20.5 per cent. The decrease in heart rate averaged 26.5 per cent.

When methoxamine was administered after atropine (Table II) pressure again rose but heart rate failed to decrease and in fact rose.

Discussion

In the presence of total sympathetic denervation heart rate decreased 26.5 per cent when arterial pressure rose 20.5 per cent following methoxamine. This suggests either (1) the efferent arc of the baroreceptor response to elevation of arterial pressure includes increased parasympathetic tone, (2) methoxamine has a direct negative chronotropic effect on cardiac pacemakers, or (3) hemodynamic alterations take place within the chambers of the heart as a result of methoxamine-induced elevation of arterial pressure which results in bradycardia because of their effect on intrinsic chronotropic stretch receptors within heart muscle.[15] If (2) or (3) were the case, methoxamine should produce bradycardia with vagal inhibition as well as when parasympathetic function is intact. The fact that methoxamine does not result in bradycardia after atropine in the sympathetically denervated individual indicates not only that methoxamine has no direct effect on heart rate but also that intracardiac hemodynamic changes consequent to methoxamine-induced elevation of pressure do not slow heart rate. In normal man, therefore, the bradycardia associated with elevations of arterial pressure is mediated, at least in part, by increased vagal tone.

The present results confirm in man observations in experimental animals that methoxamine has no direct effect on heart rate. Not only is heart rate unaffected by methoxamine in the isolated heart of rabbit[16] and dog,[17] but neither the intracoronary injection of methoxamine in innervated dog hearts nor the systemic administration of methoxamine in dogs whose hearts have been denervated affects heart rate.[18]

Reports on the effects of methoxamine on intracardiac pressures and volumes indicate that methoxamine is associated with increased atrial pressures and increased end-diastolic ventricular dimensions.[19,20] This suggests that if methoxamine were to affect heart rate secondary to changes in intracardiac hemodynamics the tendency would be for the heart rate to increase rather than decrease.[15] That methoxamine does not increase heart rate in the normally innervated heart is probably because of more powerful negative chronotropic influences initiated by baroreceptor stimulation. However, the increase in heart rate noted in the present study when methoxamine was administered during complete cardiac denervation may represent activation of intrinsic stretch receptor reflexes within the heart consequent to peripheral vasoconstriction.

Other studies have shown that the bradycardia produced by methoxamine is decreased or abolished by atropine[21,22] and by vagotomy.[18] These studies have concluded that the vagus nerve was, therefore, essential to the development of methoxamine-induced decreases in heart rate. In the absence of sympathetic denervation, however, these studies could not eliminate the possibility that decreases in sympathetic tone also contribute to the development of

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tion differences which are also reflected in the fact that the degree of bradycardia after methoxamine could not always be related with precision to the degree of elevation of arterial pressure

It is interesting to note that in the present study methoxamine was a more effective vasopressor after atropine This may have been because the increase in heart rate observed when methoxamine was administered after atropine resulted in an increase in cardiac output while the bradycardia produced by methoxamine in the absence of atropine was associated with a decrease in output.[14]

The magnitude of change in heart rate after combined sympathetic and parasympathetic denervation in the present study confirms the conclusion based upon data obtained under similar circumstances that resting heart rate in normal man is determined by both sympathetic and parasympathetic influences but that the latter predominate [14]

The present investigation demonstrates that there is a vagal component in the chronotropic response to acute baroreceptor stimulation in man It does not eliminate the possibility that the reflex bradycardia normally associated with baroreceptor stimulation may also be contributed to by a simultaneous decrease in sympathetic activity The present study also does not provide data either on the inotropic responses to baroreceptor activity or on vagal participation in the chronotropic response to chronic or subacute elevations of arterial pressure.

Summary

The vagal component of the chronotropic response to baroreceptor stimulation in normal man was evaluated by measuring responses of heart rate and arterial pressure to the intravenous administration of the alpha-adrenergic stimulator methoxamine in the presence of total preganglionic sympathetic denervation produced by spinal anesthesia. Mean arterial pressure increased an average of 20 5 per cent with methoxamine This was associated with a 26 5 per cent decrease in heart rate. Methoxamine induced bradycardia observed during sympathetic denervation was abolished when total sympathetic denervation was combined with parasympathetic inhibition (atropine) It is concluded that in normal man vagal parasympathetic impulses contribute to the development of the reflex bradycardia associated with elevation of arterial pressure.

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The failure of triggered pacemakers

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Two different modes of cardiac pacing exist. The first is much the older and is totally insensitive to cardiac action. This —*the asynchronous*—mode is unvarying in its rate unless manipulated by physician or user and is most satisfactory when little or no spontaneous ventricular activity exists or when ventricular activity can be totally suppressed by the pacemaker rhythm at normal (60 to 80 beats per minute) rates.

The triggered pacemakers are sensitive *to cardiac activity and modify their own* stimulation of the heart in response to cardiac activity, either atrial or ventricular. The first introduced, the atrial synchronous pacemaker, was intended to mimic physiologic *atrioventricular (A-V) conduction in* the presence of complete heart block and provide the benefits of the atrial contribution to ventricular filling and variation of cardiac rate with activity. The atrial synchronous *pacemaker is under most (though* not all) circumstances sensitive only to atrial activity.

The second subgroup of triggered pacemakers can be called noncompetitive; they were *designed to avoid competition with* spontaneous ventricular activity, both conducted and idioventricular in origin. These pacemakers are of two varieties. The first is inhibited in its output in the presence of cardiac activity (demand) and the second emits its *impulse into the absolute refrac*tory period of a ventricular contraction. In the absence of spontaneous cardiac activity both establish a predetermined automatic rate. Both of these varieties of *pacemaker were designed to reduce the inci*dence of sudden and unexplained death associated with asynchronous pacing competing with ventricular activity and producing ventricular fibrillation. The ven*tricular inhibited (demand) pacemaker was* also to have a greater longevity in the presence of A-V conduction as long periods might elapse when only the pacemaker sensing circuit would be operative and not *both the sensing and stimulating circuits.*

The introduction of noncompetitive pacemakers was thus accompanied by prediction of reduction of mortality rates of competitive ventricular fibrillation[1] and greater *longevity of the unit.[2] If the pacemaker did* not emit impulses for prolonged periods while the patient was in sinus rhythm.

Neither event has yet occurred. Noncompetitive pacemakers have fallen short *on both counts and have contributed prob*lems previously unknown to asynchronous pacemakers, of *sensitivity to extraneous* electrical and electromagnetic interference and arrhythmias associated with normal

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and abnormal function of the triggered pulse generator and its electrode.

Sudden death

Numerous reports have indicated that pacemaker stimuli can produce ventricular fibrillation when these stimuli fall during the *vulnerable period* of ventricular repolarization especially in the presence of myocardial anoxia,[1] acute myocardial infarction, or drug intoxication. Others suggested more sudden and unexplained deaths in the presence of fixed-rate pacing and spontaneous competitive rhythm, either conducted or ventricular.[1] In the authors' series, unexpected deaths were more frequent in those patients with noncompetitive pacemakers than in those with asynchronous pacemakers (Table I).

Whenever possible, the authors have investigated all instances of death of the patients with an implanted cardiac pacemaker, both anticipated and sudden and unanticipated. The cause of death was carefully ascertained and documented. For each death an effort was made to perform an autopsy and to study the pacing system for (1) condition of the electrode and the adjacent myocardium and contact between the two, (2) integrity of the electrode, and (3) function of the pacemaker. On the basis of antemortem clinical evaluation and the postmortem condition of the pacing system, death was attributed either to pacemaker malfunction, to demonstrated nonpacer etiology, or to unknown causes.

In the absence of permission to perform a full autopsy examination, permission to remove the pacemaker was sought. Its recovery often indicated the cause of death. In the absence of any autopsy permission the corpse was observed (if possible) in the following manner: (1) for the appearance of pacemaker emissions at the usual rate (Fig. 1) (if the deceased was in our hospital morgue, a full electronic analysis of pacemaker function was performed); (2) for response to a noncompetitive pacemaker subjected to external triggering; and (3) x-ray of the chest.

If pacemaker artifacts appear at the automatic rate, if the unit triggers properly, and if electronic analysis is satisfactory, normal pacemaker function is demonstrated and the cause of death must be laid elsewhere. When pacemaker function was normal or unknown, without other information, a death was considered sudden and undocumented. With this analysis, few patients have gone undocumented and the authors have not been able to demonstrate a greater mortality rate in patients with asynchronous pacemakers, whether with demonstrated competition or not, compared to the noncompetitive group. We have observed the onset of ventricular tachyfibrillation in those with implanted asynchronous pacemakers and later in the same patients with a demand (ventricular inhibited) pacemaker in place and functioning.[1] Sudden death occurs with or without a pacemaker in place. Only 24 of 105 deaths of our patients with implanted cardiac pacemakers fall into the undocumented category. Pacemaker induced ventricular fibrillation *may occur more frequently* in those with asynchronous pacemakers because of the propensity of all pacemaker patients to develop additional cardiac disease; the incidence is sufficiently small as to be undiscernible even in a series of 700 patients.

The incidence of sudden death unrelated to pacemaker malfunction or competitive ventricular fibrillation is as high in those with asynchronous pacemakers as in those with noncompetitive pacemakers—probably because the degree of illness of those patients with intermittent heart block is relatively similar to that of those with complete heart block.

Of 127 patients implanted with pacemakers during the year May 1, 1967, to April 30, 1968, 54 per cent received trig

Table I. Permanent implant pacemakers—undocumented deaths

Pacer type	With competition	Without competition
Asynchronous	1	9
Atrial synchronous	1	0
Noncompetitive	0	13
Total	2	22

*Not synchronous at time of death.

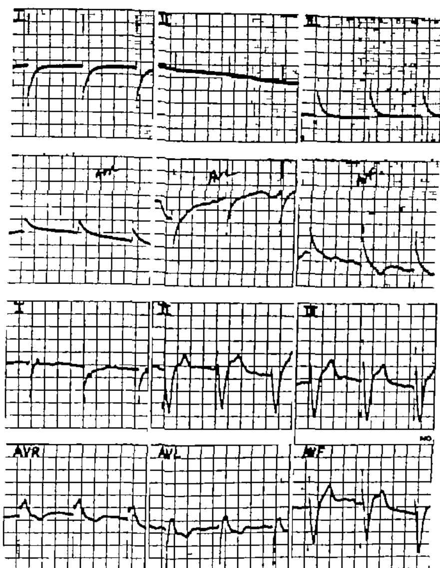


Fig 1 The upper six tracings represent the ECG limb leads after the patient death the lower six, the limb leads before death. While there is no evidence of myocardial response on the upper tracings, the pacemaker rate is constant and the artifacts are present, indicating intactness of the lead system. Pacemaker malfunction seems unlikely

gered pacemakers. Twenty nine per cent (37 patients) of the entire group died by the end of two years of follow up maintaining the same numerical relationship in death as during implantation (19 triggered 18 asynchronous) no greater mortality rate was seen in one group or the other While it is possible and perhaps even probable that *competitively* produced ventricular fibrillation contributes to death after pacemaker implantation our data do not support this conclusion

In the presence of a normally functioning pacemaker competitive activity can occur As the information developed in this communication will indicate unsatisfactory triggering and consequent competition may exist without pacemaker malfunction or only partial and apparently inconsequential malfunction

Sensitivity to arrhythmia

Asynchronous pacemakers do not respond to cardiac signals to modify pacemaker activity Triggered pacemakers do In so doing they may (1) be sensitive to abnormal cardiac activity and magnify already existent arrhythmias[10] or (2) respond *in a way that does not allow usual* cardiac drug therapy to be effective [11]

1 Arrhythmias such as multiple premature ventricular contractions may force a *ventricular synchronous pacemaker* into a competitive mode of operation as it must discharge its impulses at no greater interval than its escape or automatic rate. If that

interval arrives when a QRS complex is finishing its depolarization a pacemaker artifact may fall on the downstroke of the T wave—the vulnerable period.[11, 14] Premature ventricular contractions can fall onto the T wave of beats induced by any variety of pacemaker Such events can be as competitively dangerous as the falling of an asynchronous artifact onto the same area.

2. Atrial fibrillation or flutter in the presence of an *atrial synchronous pacemaker* forces an undesirable tachycardia as the pacemaker may respond at rates of 120 or 140 beats per minute. If these tachycardias cannot be controlled by drug therapy directed at the atrium efforts at increasing the degree of A V block with digitalis will fail should the arrhythmia not respond to cardioversion removal of the pacemaker may be required for its elimination

An *atrial synchronous pacemaker* (as the *ventricular synchronous* above) must emit impulses periodically With the failure of atrial activity a premature atrial contraction or unsensed atrial P wave the pacemaker may be forced into competitive activity.[16] This is especially true if periods of normal A V conduction have been allowing synchronization to the QRS complex rather than the P wave.[18]

Pacemaker longevity

It has been claimed that the *ventricular inhibited* (*demand*) pacemaker will be more conservative of battery energy than the *asynchronous ventricular synchronous* or *atrial synchronous* pacers, because many of the intermittent heart blocks would not require pacing for much of the time, and that this conservation would be translated into *increased* pulse generator longevity.[4] As an example the amplifier circuit in the American Optical Company's Cardiocare pacemaker draws only 3 microamperes (μA) continuously when it is not pacing and 30 μA continuously when it is pacing continuously (whether or not the pacemaker output circuit is operative, the amplifier-sensor circuit is always operative) The Medtronic Demand No. 5841 (the only demand unit of that manufacture for which longevity data are available) draws 14.5 μA continuously when not pacing and 33 μA when pacing continuously The Cordis Ectocor a ventricular synchronous unit, increases its rate of impulse emission with the return of spontaneous ventricular activity It has a minimum rate of emission of 70 beats per minute and a minimum continuous drain of 34 μA. As spontaneous rate increases, the continuous drain increases (Table II)

Under these circumstances, the difference in battery drain of two *noncompetitive* units would be greatest. An Ectocor functioning in the presence of a spontaneous cardiac rate of 85 beats per minute drains 38 μA continuously while a Medtronic Demand unit set at an automatic rate of 60 or 70 impulses per minute would be draining at 14.5 μA continuously That these two units have almost identical longevity patterns and that the American Optical Cardiocare pacemaker (with a drain of 3 μA under the same circumstances) has an average longevity 45 per cent less than either of the other two is a measure of the importance of other design factors in pacemaker longevity

Each commercially available pacemaker listed in Table II uses identical mercury zinc cells of 1 000 mA hour rating as the energy source. All but the General Electric Standby use them in a grossly similar fashion—five cells in series to produce a battery with an open circuit output of 6.5 to 6 7 volts. Only the General Electric Standby uses six cells in series to produce a battery of 8 0 volts open-circuit output. The drain from the battery of cells varies and yields some clue concerning the varying longevities of the pulse generators (Table III)

Cordis Ventricor 111B and 111C are similar designs of asynchronous pacemaker differing largely in the addition of a rate-decreasing feature in the circuit of 111C which heralds exhaustion of the battery Longevity has been similar except that all 111B units reaching 30 to 31 months were electively removed whereas 111C units were allowed to run to actual exhaustion Comparison of 111C with a continuous drain of 22 μA and Medtronic 58 0C with its drain of 33 μA yields some suggestion concerning the small but distinct difference in longevity between the two units.

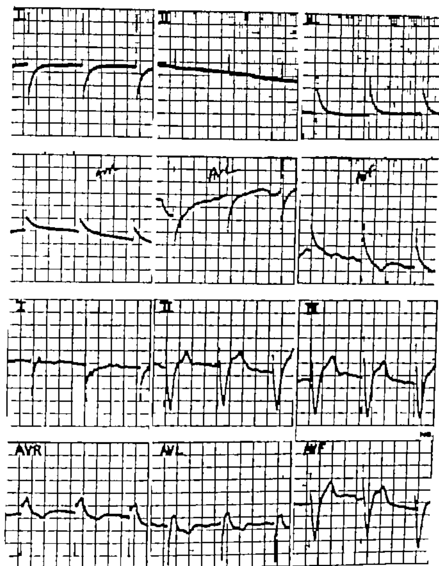


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Table II. Continuous battery drain (in μA) (500 ohm load). This table was produced with information provided by the manufacturers enumerated

Pacemaker manufacturer Model No.	Per cent of time pacing		
	0	50	100
Medtronic 5870C	NA	NA	33.0
Medtronic 5870	NA	NA	17.0
Medtronic 5841	14.5	24.5	33.0
Medtronic 5842	12.5	19.5	26.5
Cordis Atricor 133	29†	36‡	44§
Cordis Ectocor 129C and E	34‖	38‡	51¶
Cordis Stanicor 143A	13	21	29
Cordis Ventricor 111C	NA	NA	22
Cordis Ventricor II 127A	17	30	42
American Optical Cardiocare No. 10660#	3.0	16.5	30
American Optical Cardiocare No. 281003#	7.5	21.5	35
General Electric A2072BA, single rate, 70BPM	NA	NA	30–32
General Electric A2072AA, dual rate			
70BPM	NA	NA	30–32
85BPM	NA	NA	35–36
General Electric Standby	10–12	20–21	30–32
Vitatron MIP 150 (asynchronous)			
70BPM	NA	NA	20
90BPM	NA	NA	28
Vitatron MIP 400R (demand)	16	28	41

NA, Not applicable. Asynchronous pacemakers stimulate the heart continuously.
†It is assumed that the cardiac rate is below the pacemaker automatic rate and that it is operating as fixed rate ... at an ... rate—60 impulses per minute.
‡It is assumed that the pacemaker is emitting impulses at an average of 85 per minute.
§Impulses are emitted at the maximum rate of the unit—123 per minute.
‖The pacemaker impulse emission rate is 70 per minute.
¶Impulses are emitted at the maximum rate of the unit—143 per minute.
#Lead is Medtronic bipolar endocardial electrode No. 5816.

The American Optical Cardiocare pacemaker had a respectably low drain while sensing only and an average or low drain during pacing. Nevertheless, because of deficiencies in circuit and encapsulant design, longevity was very short. Aside from that unit, the shortest longevity has been achieved by the Cordis Atricor (atrial synchronous) and Ectocor (ventricular synchronous). Both have high battery drain even at minimum battery expenditure and these rise rapidly well above that of other pacemakers when functioning in the triggered mode (Table II). A hopeful sign is the effort in Medtronic Demand No. 5842 and Cordis Stanicor No. 143 toward reduction of battery drain during operation, accomplished for the Medtronic unit in part by reduction of pulse duration from 1.7 to 0.85 msec.

Unfortunately, all these efforts at conservation of energy can be only partially successful because of the internal discharge of mercury zinc cells at body temperature causing accelerating deterioration with longer pacemaker residence in the body (Fig. 2).

As battery technology increases, the limited energy supply contained within each pacemaker may become unimportant to longevity, but such is not presently the case. Of greater importance to longevity are (1) satisfactory design of a cardiac pacemaker and avoidance of circuit designs which shorten longevity, (2) use of the appropriate pacing mode, i.e., an asynchronous pacemaker when noncompetitive or atrial synchronous pacing is not required and does not add to the therapeutic result, (3) design of pacemaker output circuits to take advantage of electrodes which have low thresholds of cardiac stimulation.[17, 18]

The authors' pulse generator longevity

Table III. Authors' data

Pacemaker manufacturer: Model No.	Longevity (mo.)		
	Average	*50 per cent fail*	*Greatest*
Medtronic 5870C	21.4	23	32
Cordis Atricor	18.1	19	31
Cordis Ectocor 129C	20.1	20.5	26
Cordis Ventricor II 127A	21.8	21	30
American Optical Cardiocare	14.3	16	21
Cordis Ventricor 111B	22.9	25	31
Cordis Ventricor 111C	24.0	25	36

*This table contains only the authors' data. The two models of asynchronous Cordis pacemakers were tested so that longevity would not be unduly shortened by our practice of routine removal of asynchronous pulse generators at 30 months. That practice caused the removal of 9 units, and of 45 in the entire followed series, 7 of which were capable of substantial continued function.

data on a total of 1,000 pulse generators has been tabulated (Table III) and indicates that each of the triggered or noncompetitive pacemakers has a substantially shorter average longevity than the asynchronous units, and that the time when 50 per cent of the pulse generators had been replaced was longer for asynchronous than triggered units, as was the maximum longevity achieved by any single unit.

Complications of pacing modes

The major complications of asynchronous pacing are the occasional occurrence of ventricular tachyfibrillation and the summation of spontaneous and paced rhythms when return of spontaneous rhythm occurs resulting in a continuous pacemaker-related tachycardia (Fig. 3). The most serious and overriding drawback to the use of asynchronous pacing is the widespread recognition that the intermittent heart block is better treated with a noncompetitive pacemaker than by an asynchronous pacemaker which has the attendant possibilities of pacemaker-induced and symptomatic premature ventricular contractions, parasystole, and tachyfibrillation.

Interference phenomena

Electrical interference phenomena have been observed with almost all cardiac pacemakers.[18] The relatively slight interference caused in the function of asynchronous pacemakers is magnified in the case of triggered pacemakers which are designed to

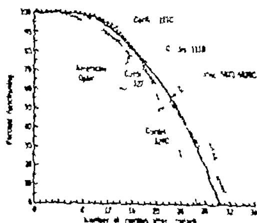


Fig. 2. A graphic comparison of the longevities of several popular pacemakers. The 50 per cent failure time for the Cordis asynchronous pacemakers (111B and 111C) is approximately 25 months; for Medtronic 5870C units, 23 months. The Cordis Standby (ventricular inhibited) 127A is 21 months and the ventricular synchronous 129C is 20.5 months. The American Optical Company Cardiocare 50 per cent failure point is at 16 months, although this represents pacemaker longevity beyond the manufacturer's recommendation.

respond to cardiac electrical activity and which therefore must discriminate between responding appropriately to cardiac electrical activity and either not at all or in a safe fashion to extraneous electrical activity.[19]

All triggered pacemakers can be made to respond to electrical interference. The variety of response is important. Ventricular and atrial synchronous pacemakers may begin to emit stimuli rapidly and

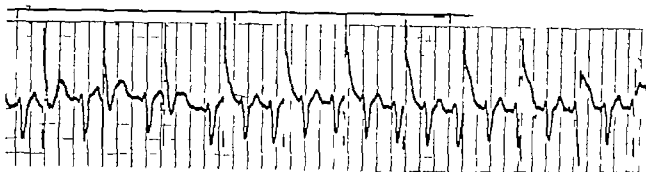


Fig 3 The idioventricular rate of 70 per minute and the asynchronous pacemaker rate of 70 per minute are additive, with parasystole and competitive pacemaker artifacts and spontaneous contractions. The total ventricular rate is about 120 per minute and irregular

erratically to the maximum rate of which they are capable *demand (ventricular inhibited)* pacemakers may respond by ceasing emission of signals. Recognizing the danger of this situation several manufacturers have responded by adding 60 cycle filtration and by converting the pacemaker from triggered to asynchronous function in the presence of 60 cycle interference The pacemakers which behave in this way are American Optical Cardiocare General Electric Standby Cordis Stanicor Cordis Ectocor and Medtronic Demand No 5842 Demand pacemakers forced into a quiescent mode in the presence of 60 cycle AC are the Medtronic Demand No 5841 and the Vitatron Demand (Table IV)

Electrode configuration

Unipolar electrodes have the negative stimulating terminal in the heart and the *positive at a distance either on or near the* pulse generator They are much more sensitive to any electrical signal because of the long electrode dipole between the anode and the cathode [21] Bipolar electrodes in which both anode and cathode are intraventricular are far less sensitive to both cardiac and extraneous signals.

Unipolar electrodes are universally sensitive to ventricular activity and if the pulse generator is operating well and the electrode is well positioned proper triggering can be anticipated Such is not always the case with bipolar electrodes, which can stimulate consistently and at a satisfactory threshold without sensing signals adequately

Both unipolar and bipolar electrodes sense the difference between the potentials existing on anode and cathode which must exceed the sensitivity of the pulse generator (usually 2 mv) in order that it respond Such a signal is almost always available from the intraventricular cathode and the extracardiac reference anode It may not be available when the anode and cathode are closely adjacent and sense essentially the same intraventricular signal

With both anode and cathode within the right ventricle two different interference phenomena may occur

1 The potential difference between anode and cathode may be inadequate to sense the QRS complex and the pacemaker will then revert to asynchronous and therefore competitive operation (Fig 4) The potential difference between the intraventricular electrodes may be determined with a well grounded electrocardiograph With the four limb leads attached the V lead is connected to the tip and proximal electrodes in turn and the electrograms are recorded They will usually be between 12 and 20 mv in amplitude Lead I (right arm and left arm) is then used to determine the bipolar potential which may be equal to or substantially less than the individual unipolar potentials and even less than the potential required to trigger a pacemaker The proper stimulating-sensing correction for such a situation is the conversion of the bipolar to a unipolar assembly [22]

2 Triggering may occur from physiologic signals other than the QRS complex Pulse generators with refractory intervals shorter than 100 msec. may recycle from a *spontaneous* QRS complex and then from its high amplitude T wave. Other T wave interference may slow the pacemaker rate if a T wave of a paced QRS complex *triggers* and *recycles* the pacemaker [23]

Table IV. Noncompetitive pacemakers

Pacer	Response to 60 Hz. A C	Tripped battery	Idiosyncrasies
Medtronic 5841	Cessation of impulses	Some models yes, some no	(1) No magnetic fixed rate (2) pacemaker bradycardia
Medtronic 5842	To automatic rate	N	Magnetic fixed rate
American Optical	To automatic rate	Yes	(1) Short life (2) frequent runaway
Cordis 143A	To automatic rate	N	Magnetic induced bradycardia
Cordis 129	To automatic rate and/or rapid and erratic impulses	N	ECG distortion
General Electric	To automatic rate	No	Magnetic induced bradycardia
Vitatron	Cessation of impulses	No	Threshold analysis possible

Atrial P waves may cycle the bipolar pacemaker especially if the proximal electrode is close to the atrium and the potential difference developed is large. Such cycling will produce an irregular rhythm which is inexplicable in terms of ventricular activity alone (Fig. 5).

False triggering may occur with either unipolar or bipolar electrodes.

1. *Triggering may occur from signals generated by a defective electrode.* A pacemaker electrode may undergo partial or complete disruption of insulation, conductive elements, or both. Should the insulation leak and the wire break, then the gap between the two fractured ends of the conductive element will be bridged by body fluid. The resistance of such an electrode will change and adversely affect the ability of the pacemaker to stimulate the heart. If the fractured metallic elements continue to lie in contact with each other, then apparently normal cardiac stimulation may continue despite a varying electrode resistance. As triggered pacemakers (except the atrial synchronous unit) use the same electrode for activating the pacemaker amplifier as well as stimulating the heart, these two functions may not be performed equally well. Sudden changes in electrode resistance can produce an electrical potential which may mimic a physiologic signal, change the pacemaker discharge rate, inhibit demand pacemaker emission, or produce improperly synchronized pacemaker emissions. The requirement of sensing and transmitting adequate cardiac signals, free of electrode-induced artifact, has been added to the need of lead integrity for stimulation.[14]

2. *Triggering may occur from signals generated by electrode polarization.* Cardiac stimulation following passage of a current through an electrode causes the establishment of two different levels of polarization in effect electric potentials, at the anode and cathode of an electrode system. As this electrode-induced potential wanes, it may persist in intensity above the sensitivity threshold of the pulse generator, in duration beyond the pacemaker refractory period. As *ventricular inhibited (demand)* pacemakers usually have short (100 to 250 msec.) refractory periods, the pacemaker may be recycled by this polarization effect when it persists beyond the return of pacemaker sensitivity. The effective refractory period may then be increased beyond its nominal duration and an apparently different refractory period may exist after paced beats (when electrode polarization exists) *and after* spontaneous QRS complexes (when electrode polarization does not exist). This has been referred to as the "double reset" phenomenon.[18]

One way of eliminating this phenomenon is the prolongation of the pacemaker refractory period. Following implantation of over 250 *ventricular synchronous and inhibited pulse generators* with a refractory period of 400 msec., this "double reset"

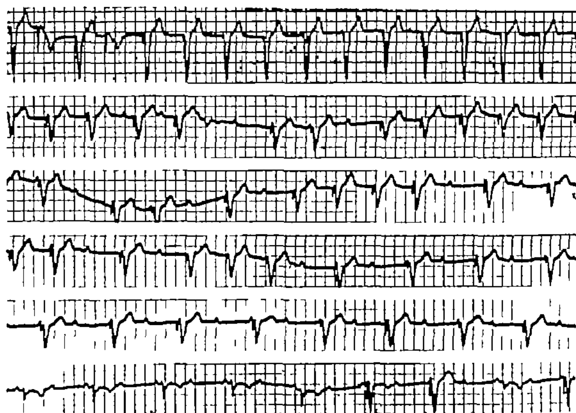


Fig 4 Cycling of this demand (Medtronic No. 5841) pacemaker occurs from QRS complexes, P waves (lines 2 3 4 and 5) and T waves (line 6)

phenomenon has not been observed Apparently this period is of sufficient duration to avoid residual electrode polarization (Fig 6)

Magnetic interference

Electrical interference has been better documented than interference by a magnetic field Virtually all triggered pacemakers (except Medtronic Model No 5841 and Cordis Atricor) have incorporated an externally activated magnetic switch for the testing of pacer output characteristics in an untriggered mode of operation In at least one model (Cordis 143A) placing the magnet over the pacemaker results in an asynchronous pacemaker rate *after* one pacemaker emission has been withheld A fluctuating magnetic field which may be produced by moving the magnet to and from the pulse generator causes a prolonged period of pacemaker quiescence (Fig 7)

Discussion

Triggered pacemakers have found great utility in cardiac pacing and dominate the field today Many patients who are well controlled with cardiac pacemakers would

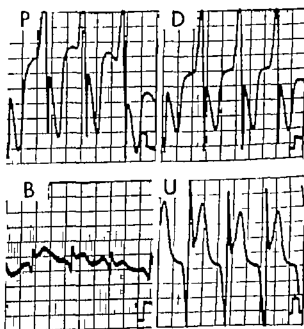


Fig 5 With failure of adequate triggering, the V lead of the ECG was used to determine the amplitude of the QRS complex sensed at the proximal (*P*) and distal (*D*) terminals of a bipolar electrode. Use of Lead I to determine the bipolar signal (*B*) reveals it to be below 2 mv Conversion of the system to unipolar operation (*U*) returns to a large intraventricular signal The rectangular marks represent 1 mv

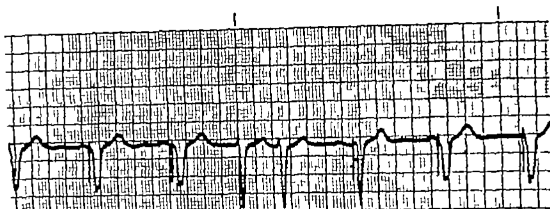


Fig. 6 The demand pacemaker (Medtronic No. 5841) automatic interval is the time between the spontaneous beat and the first paced beat. The interval between any two beats is longer in this instance result of the double reset of the pacemaker timing circuit.

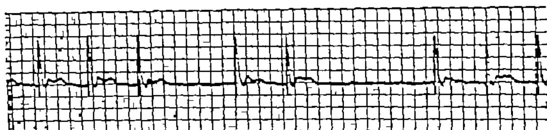


Fig. 7 The pacemaker implanted is Cordis Stanicor (143A7). This pacemaker contains a magnetic switch for conversion from triggered to asynchronous operation. A fluctuating magnetic field is produced by moving magnet alternately to and from the implanted pacemaker Total pacemaker inactivity occurs while the magnet is moving

not be paced were it not for the development of noncompetitive pacing (Triggered pacemakers have held out the hopes of a more physiologic approach to cardiac stimulation with atrial synchrony and of safer stimulation with noncompetitive pacing and greater pacemaker longevity with a unit which withholds its emissions in the presence of spontaneous cardiac activity None of these hopes has been fully realized.) Atrial synchrony in the older patient has been difficult to control in the presence of atrial arrhythmia the incidence of sudden death has not been demonstrated to be significantly lower in patients with noncompetitive compared to asynchronous pacemakers and pacemaker longevity for triggered pacemakers has so far proved to be substantially shorter than for asynchronous units. Pulse generator replacement is a cause of hospitalization with a wound complication rate often higher than that for primary pacemaker implantation.[24]

While four pacing modes exist (*asynchronous ventricular synchronous ventricular inhibited (demand) and atrial synchronous*) none has demonstrated clear superiority over the others for routine use each has its virtues and flaws and the use of one to the exclusion of the others is unwarranted The young patient with heart block and a healthy myocardium should have an atrial synchronous pacemaker the patient in fixed complete heart block an asynchronous pacemaker the one with intermittent block and a fairly rapid spontaneous rate (80 to 90 beats per minute) a ventricular inhibited (demand) pacemaker and the patient with only occasional spontaneous beats and possibly subjected to substantial electrical interference, a ventricular synchronous pacemaker

The superior interference rejection of the bipolar electrode has been largely overcome by improvements in circuit design of unipolar pulse generators. The incidence of improper response to physiologic signals detected by bipolar electrodes is greater

than the problem of interference sensitivity

Pacemaker variation is still necessary and perhaps desirable. If the difficulties associated with shortened longevity elec tromagnetic interference and the effects of electrode malfunction can be resolved the utility of triggered pacemakers may be enhanced Under present circumstances a distinct role for the asynchronous pace maker still exists

Summary

Noncompetitive pacemakers had been expected to prolong pacemaker longevity and reduce patient mortality rates com pared to asynchronous pacemakers Neither has occurred Mortality rates are equal to those for asynchronous pacemakers and pacemaker longevity has been substantially shorter Problems unique to triggered pace makers of electromagnetic interference pacemaker induced arrhythmias, inadequa cies in sensing physiologic signals with *bipolar* electrodes and artifacts mimicking the normal cardiac signal produced by normal and partially defective electrodes have occurred All of these factors have limited the utility and in some instances the safety of triggered pacemakers.

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Mitral stenosis and insufficiency: A complication of healed bacterial endocarditis

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Acquired stenosis of the mitral valve is almost always the result of rheumatic valvulitis. However, in rare instances, it may result from obstruction of the valve orifice by bacterial vegetations.

This report is comprised of three cases of mitral stenosis in which calcified vegetations obstructed the valve orifices. Mitral insufficiency was also present in each case.

Case 1

A 34-year-old Puerto Rican man entered the hospital because of heart failure of three months' duration. Two months prior to admission he was treated with penicillin for a lung trouble. There was no history of rheumatic fever or heart murmurs. Physical examination revealed an enlarged heart with a regular rhythm. He had a Grade II/VI holosystolic apical murmur and a low-pitched Grade II/VI diastolic murmur. An electrocardiogram showed a P mitral pattern and right axis deviation with strain. The clinical impression was mitral stenosis and insufficiency secondary to rheumatic heart disease. Two weeks after admission the patient developed pleuritic pain, shortness of breath, and right-sided pleural effusion. Despite treatment with ampicillin, digitalis, and diuretics, his condition deteriorated and he died shortly afterward.

Necropsy revealed multiple pulmonary emboli and infarcts and an organizing bronchopneumonia. The lungs also showed chronic passive congestion. The heart displayed biventricular hypertrophy (450 grams). The right atrial appendage contained an organizing thrombus and the left atrium was conspicuously dilated and thickened. The mitral valve measured 9.5 cm. in circumference. A cauliflower-shaped vegetation, measuring 2 cm. in diameter was adherent to the posterior mitral leaflet. It protruded into and obstructed the valve orifice resulting in stenosis (Figs. 1 and 2). Histologically the vegetation was entirely calcified. Stains, smears, and cultures for microorganisms were negative. A healed ulceration was found on the posterior leaflet at the site of the vegetation attachment. The uninvolved anterior leaflet showed thickening, fibrosis, and vascularization with fused and shortened chordae tendineae. These changes of healed rheumatic endocarditis in combination with the valvular deformity at the site of the vegetation attachment resulted in insufficiency of the mitral valve.

Case 2

A 60-year-old white woman with known rheumatic heart disease since age 12 presented with increasing shortness of breath of two weeks' duration. Two years prior to admission she was hospitalized for bronchopneumonia and mild congestive heart failure. She responded well to treatment with penicillin, digitalis, and diuretics. The latter were continued to the time of this admission. Physical examination revealed an enlarged heart with an intermittently irregular rhythm and a Grade III/VI apical holosystolic murmur. The first heart sound was accentuated. There was a third heart sound and an opening snap at the apex, followed by a Grade II/VI early diastolic low-pitched murmur. An electrocardiogram (ECG) showed atrial fibrillation and right axis deviation with strain. Rales were heard at both lung bases. The liver extended 5 cm. below the right costal margin. The clinical impression was mitral insufficiency and stenosis secondary to healed rheumatic endocarditis. Shortly after admission the patient complained of severe abdominal pain, became progressively disoriented, and died.

At autopsy an acute hemorrhagic infarction of the jejunum and ileum was found. The heart exhib-

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Fig *1* Caul flower shaped vegetation obstructing *the mitral orifice* (Case 1)



Fig *2* Calcified vegetation on the posterior leaflet of the mitral valve Note thicken ng of the valve fusion and shorten ng of chordae tendineae (Case 1)

lted biventricular hypertrophy (400 gram) The left atrium was d lated and thickened The mitral valve measured 7 0 cm. i circumference Attached to ts posterior leaflet was a calcified polypoid vegetation measuring 1 8 cm. n diameter It extended into the left atrium and obstructed the valve orifice resulting in m tral tenos M croscopically the *vegetation was calcified and fibrotic* examination for microorganisms was negative The posterior mitral leaflet nd the chordae tendineae below the excrescence were deformed The latter displ yed several adhere t calcified vegetations meas ring up to 0.5 cm. in diameter (F g 3) The remainder of the val e was thickened fibrotic, and vascularized w th *fusion and hortening of the chordae tendineae* The m tral ulus wa not calcified These lesions of healed rheumatic endocarditis, together with the valvular deformity associated with the veget tions, resulted in mitral insufficiency The lung showed severe acute pulmonary eden acute and chronic passive congest on and arteriosclerosis.

Case 3

An 81 year-old wh t m i entered the hospital with severe shortness of breath nd progressive disorientation of one week d r tion Sixteen years prior to admission a abdominal perineal resection was performed for carcinoma of the rectum Eight *months* prior t this hosp talization the patie t had an ileocolic resection nd colostomy *for* volvulus of the terminal ile m. At that time he was treated with a f ll course of penicillin and treptomycin. He gave no *history of rhe matic fever or heart murmurs.* On physical examination the heart was enl rged and had an intermittently irregular rhythm. No murmurs were heard Panlobular coarse and crepitant rales were heard over the lungs. An ECG showed atrial fibrillation nd right axis deviation w th stra n. Before the physical examination could be completed *the* patient had a cardiac arrest attempts t resuscitation were unsuccessful

Necropsy revealed acute obstruction of the ampulla of Vater by mixed gallstones. The heart showed biventricular hypertrophy (375 grams) The left atrium was d lated and thick ned The mitral valve measured 9 0 cm. in circumference. A calcified and fibrotic *vegetation, which measured 1.5 cm. in* diameter was adherent to the posterior leaflet of the mitral valve It partially occluded the mitral orifice and produced stenosis (Fig 4) Stains smears, and cultures for microorganisms were negative. The portion of the leaflet directly beneath the excrescence displayed healed ulceration. The remainder of the valve was thickened vascularized, and fibrotic with fusion and hortening of the chordae tendineae. The mitral nnulus wa not calcified. The above stigmata of healed rheumatic endo*card tis, in addition to the healed ulceration of the* posterior leaflet, resulted in insufficiency of the mitral valve. The lungs howed severe acute pulmonary edema, acute and chronic passive congestion, and moderate arteriosclerosis.

Discussion

The patients described in this report had congestive heart failure and the clinical manifestations of mitral stenosis and insufficiency The latter included a holosystolic apical murmur and a diastolic low pitched murmur with an opening snap (Cases 1 and 2) ECC s showed a *I mitral* pattern (Cases 1 and 2) with right axis deviation and strain (Cases *1 2* and 3) *Clinically Cases 1 and 2 were thought to* have mitral stenosis and insufficiency sec ondary to previous rheumatic valvulitis *while evaluation of Case 3 was not com* plete at the time of death

In each case the autopsy revealed vege *tations on the posterior* leaflet of the mitral valve They obstructed the mitral orifice by dint of their size and position T d

despite a normal circumference of the valve ring in two cases (Cases 1 and 3) and a minimally diminished circumference in one (Case 2). The normal or only slightly altered size of the mitral valve in each case strongly suggests that the stenosis was due to obstruction of the lumen by the vegetation rather than contraction and destruction of the valve leaflets by rheumatic disease. The vegetations were distinguished by their large size, cauliflower shape and the presence of underlying valvular ulceration and deformity. Histologically they were calcified and fibrotic stains, smears, and cultures for microorganisms were negative. These findings are consistent with healed bacterial endocarditis.

Harbitz, Osler and Libman in the preantibiotic era reported cases of healing and healed bacterial endocarditis and described calcification as a prominent feature of the reparative process. Calcification of the vegetations of Brucella endocarditis is common and when prominent is indistinguishable from calcific aortic stenosis, to which it may be etiologically related. Calcification and fibrosis of vegetations is also commonly seen in cases of treated subacute bacterial endocarditis.[7] When this reparative process involves the valve leaflet there may be sufficient deformity to result in mitral insufficiency. Rarely active bacterial endocarditis can lead to mitral stenosis as well. This occurs when polypoid vegetations are sufficiently large to obstruct the valve orifice. I was unable to find previously described cases of mitral stenosis resulting from persisting calcified bacterial vegetations.

All the patients reported here had previously received antibiotics. This may have accelerated or even initiated healing of an unrecognized bacterial endocarditis. Unsuspected healed bacterial endocarditis with extensive calcification should be included in the differential diagnosis of mitral stenosis and insufficiency particularly in view of the current widespread use of antibiotics.



Fig. 3. Calcified vegetations adherent to the posterior mitral leaflet and its associated chordae tendineae (Case 2).



Fig. 4. Polypoid vegetation adherent to the posterior mitral leaflet (Case 3).

Summary

Three cases of mitral stenosis and insufficiency produced by clinically unsuspected healed bacterial endocarditis are described. The vegetations in each case were calcified devoid of inflammation and microorganisms, and associated with underlying valvular destruction. The uninvolved valve in each heart showed the stigmata of healed rheumatic valvulitis. In light of the widespread use of antibiotics clinically unsuspected cases of healed bacterial endocarditis and its sequelae may be encountered more frequently.

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A double-blind double cross-over trial of prenylamine in angina pectoris

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Prenylamine is used widely for the management of angina pectoris. Several controlled studies have demonstrated that the drug given at proper doses, reduced the frequency of anginal attacks except for one trial in which the observed differences between the results of placebo and prenylamine medication were not considered significant.[4]

Discrepancies in the findings of controlled drug trials in angina pectoris are well known and emphasize the difficulties besetting the clinical evaluation of antianginal agents. The problems arising from the capricious nature of the disease have only recently been pointed out again together with the need for elaborate trial designs to obviate or reduce at least some of the factors that could affect the relevance of the findings.

To assess the efficacy of prenylamine under even more stringent conditions than those used previously a double-blind double cross-over study was carried out in office patients with angina pectoris.

Patients and trial design

The patients were selected from among those visiting the investigators offices. The most important criterion for inclusion in the trial was a history of recurrent typical anginal attacks, characterized by the nature, site, and radiation of pain, which had to be elicitable by exertion and relievable by rest with or without nitroglycerin. The diagnosis was to be further supported by electrocardiographic changes suggestive of ischemic heart disease and appearing at rest or after exercise. No restrictions were imposed with regard to age and sex.

Each patient was to participate in the trial for 36 weeks. The first phase of 12 weeks served primarily to establish the maximal daily dose of prenylamine that the individual patient could well tolerate. Done in a single-blind manner this part of the study began with a two-week placebo period. During the subsequent six weeks the patient was given active drug (prenylamine lactate, 60 mg of free base per tablet) at an initial dose of 240 mg

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Table I. Distribution of patients among groups

Group	No. and sex of patients	No. of patients		Criteria for inclusion
		Sequence $A_1N_1A_2N_2$	Sequence $N_1A_1N_2A_2$	
I	17 (11 M, 6 F)	8	9	Complete records with correct intervals
II	27 (20 M, 7 F)	17	10	Complete records; at least one interval deviating by one or more days from correct number of days; medication uninterrupted
III	6 (5 M, 1 F)	1	5	Incomplete double-blind period, but adjacent A and N sequences available
IV	19 (15 M, 4 F)			Terminated trial in single-blind or early in double-blind period or highly irregular and confusing records

(four tablets). The dose was then raised or lowered within a range of 120 to 300 mg depending on its tolerability. The dose-titration period was followed by another four weeks of placebo administration to avoid the possibility of a carry-over effect of the active drug into the next phase of the trial.

The second phase lasted 24 weeks and was designed as a double-blind, double cross-over study. Each patient received the active drug (A) and the placebo (N) in alternating sequences of six weeks. The sequences could be either prenylamine-placebo-prenylamine-placebo ($A_1N_1A_2N_2$) or placebo-prenylamine-placebo-prenylamine ($N_1A_1N_2A_2$). The daily number of prenylamine or placebo tablets was that found in the preceding dose-titration period as the maximal well-tolerated dose. The investigators were unaware of the order of the sequences, nor did they know that the active drug and the placebo were to be crossed-over twice.

Office visits of the patients were spaced at two-week intervals during the entire 36 weeks of the trial. At each visit the patients were given a supply of prenylamine or placebo sufficient for two weeks. The unused tablets of the preceding two weeks had to be returned. In addition to the medication the patients also received a card on which they had to record daily the frequency of anginal attacks and the number of nitroglycerin tablets taken in the appropriate two-week interval. The cards also contained spaces for entering the pertinent comments regarding the severity of the attacks (more severe, less severe, same), the distance the patient could walk (more, less, same), and how he felt (better, worse, same).

The investigator examined blood pressure and heart rate during the visit. On a case report form he entered side effects experienced by the patient, any intercurrent diseases, and other items of interest for the trial. Antianginal drugs other than prenylamine and nitroglycerin were not used.

Electrocardiograms (ECG's) at rest and frequently after exercise were recorded at the beginning of the single-blind period and 8 and 12 weeks later, as well as 6, 12, 18, and 24 weeks following the beginning of the double-blind period.

Results

Forty-four (31 men, 13 women) of the 69 patients (51 men, 18 women) who had consented to participate in the study finished it and returned complete records. Seventeen of these records were perfect. The remaining 27 contained minor deviations from the prescribed number of days in at least one placebo or prenylamine interval, but medication was at ... ex-

Table II. Frequency of anginal attacks, number of nitroglycerin tablets, and average pulse rates in combined prenylamine ($A_1 + A_2$) and placebo ($N + N_2$) periods. Sequence $N_1A_1N_2A_2$

Group	Pt. no.	No. of anginal attacks		No. of nitro. tab. taken		Average pulse rate		No. of days of treatment	
		A + A	N + N	A + A	N + N	A + A	N + N	A + A	N + N
I	1	3	12	0	7	61	64	84	84
	2	23	27	15	11	63	62	84	84
	3	0	5	0	5	69	70	84	84
	4	23	37	29	41	76	76	84	84
	5	6	11	5	12	62	64	84	84
	6	3	2	1	2	43	54	81	84
	7	13	39	14	37	60	80	81	84
	8	163	210	181	247	65	67	84	84
	9	32	34	13	29	53	66	84	84
Subtotal	9	266	377	258	418	552	603	756	756
P		<0.01		0.01		<0.005			
II	10	33	45	12	42	87	90	88	84
	11	1	6	2	8	81	74	81	84
	12	85	264	79	263	67	72	82	86
	13	646	659	641	673	62	80	87	85
	14	4	9	8	18	68	78	84	83
	15	50	111	0	18	62	70	83	88
	16	96	110	6	0	68	73	84	81
	17	27	41	24	39	68	74	84	83
	18	44	93	50	91	76	77	84	83
	19	635	608	636	597	76	82	85	83
Subtotal	10	1,621	1,934	1,458	1,751	715	770	842	841
P		<0.02		0.1		<0.025			
Total	19	1,887	2,311	1,716	2,169	1,267	1,373	1,598	1,957
P		<0.01		<0.01		<0.005			

uninterrupted. Six other patients returned records that were incomplete with, however, one adjacent prenylamine and placebo sequence present. The remaining 19 patients terminated the study prematurely or submitted unsatisfactory records. Depending on the quality of the records and the completion of the study, the patients were divided into four groups which, in turn, were subdivided in accordance with the two possible sequences $A_1N_1A_2N_2$ and $N_1A_1N_2A_2$. Table I shows the number of patients in each group and subgroup as well as the criteria used for inclusion in the particular group.

Table II presents the number of anginal attacks and nitroglycerin tablets taken for the combined prenylamine ($A + A_2$) and placebo periods ($N + N_2$) and the number of days reported by the patients of Groups I and II who started with placebo (sequence $N_1A_1N_2A_2$). Table III lists the same information for those patients who started with prenylamine (sequence $A_1N_1A_2N_2$). Both tables, in addition, show the pulse rates averaged for the prenylamine and placebo periods.

For the statistical analysis the Wilcoxon matched-pair signed-rank test was selected because individuals differ in their responses to drugs not only in their averages but also in the variance. Use of a nonparametric test without the assumption of equally distributed or normally and equally distributed random variables precludes the danger inherent in other tests that a few exceptional responders might dominate the analysis. To allow for the qualitative

Table III Frequency of anginal attacks number of nitroglycerin tablets and average pulse rates in combined prenylamine ($A_1 + A_2$) and placebo ($N_1 + N_2$) periods Sequence $A_1N_1A_2N_2$

Group	Pt no	No of anginal attacks		No of nitro tabs taken		Average pulse rates		No of days of treatment	
		$A_1 + A_2$	$N_1 + N_2$	$A_1 + A_2$	$N_1 + N_2$	$A_1 + A_2$	$N_1 + N_2$	$A_1 + A_2$	$N_1 + N_2$
I	20	42	51	30	28	68	83	84	84
	21	59	84	82	102	65	68	84	84
	22	77	461	76	461	73	81	84	84
	23	588	828	588	829	62	63	84	84
	24	1	4	2	6	62	77	84	84
	25	0	0	0	3	63	64	84	84
	26	1	15	0	4	72	78	84	84
	27	5	13	82	92	—	—	81	84
Sub total	8	773	1 456	860	1 525	465	514	672	672
p		<0 01		<0 02		0 01			
II	28	12	23	1	4	—	—	83	84
	29	101	135	22	26	77	78	84	83
	30	8	12	20	35	65	73	79	87
	31	7	11	12	16	57	62	85	77
	32	397	425	466	482	79	75	85	84
	33	17	13	7	4	65	76	84	85
	34	259	345	47	83	55	66	83	84
	35	19	17	8	5	62	74	80	80
	36	191	216	76	126	49	65	84	83
	37	59	69	183	193	71	80	83	84
	38	0	3	0	4	70	79	80	84
	39	38	46	7	7	88	90	87	93
	40	90	97	186	198	60	55	87	88
	41	8	71	0	0	62	76	80	83
	42	60	90	116	139	59	61	82	86
	43	9	28	10	35	76	80	83	80
	44	13	132	13	132	81	89	81	83
Subtotal	17	1 288	1 733	1 174	1 489	1 076	1 179	1 417	1 440
p		<0 01		<0 01		<0 005			
Total	25	2 061	3 189	2 034	3 014	1 541	1 693	2 089	2 112
p		<0 01		<0 01		<0 005			

differences in the patient s records, and thus for even more stringent criteria in the statistical analysis the results of the two groups of patients and again for the two possible treatment sequences within each group were evaluated separately The small irregularities in the lengths of the treatment intervals recorded by the pa tients constituting Group II were corrected by dividing the number of attacks or nitroglycerin tablets by the number of days reported per interval

As Tables II and III show the number of anginal attacks and nitroglycerin tablets during the combined prenylamine periods was significantly lower than during the combined placebo periods. The mean per centage reduction in the daily number of anginal attacks during the prenylamine periods as compared to that during placebo periods was about 38 per cent the median percentage reduction about 30 5 per cent

To find out whether prenylamine was similarly effective in those patients whose deficient record keeping had ruled out a formal statistical analysis the daily aver age number of anginal attacks and nitro- glycerin tablets was calculated for both

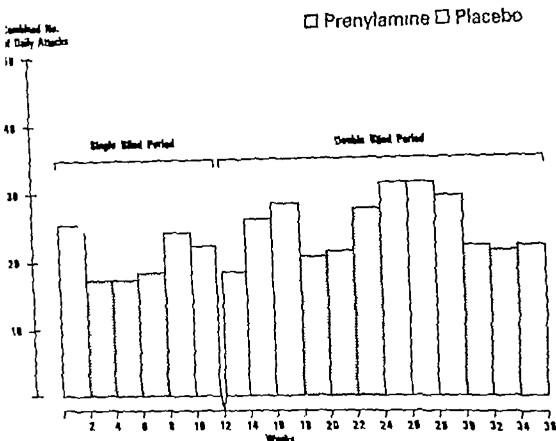


Fig. 1. Combined daily number of anginal attacks in patients of Groups I and II (n = 19) during single-blind and double-blind periods of trial. Double-blind sequence $N_1A_1N_2A$

types of medication. In the seven patients that could be evaluated because of an adjacent prenylamine and placebo sequence (Group III) the daily average number of anginal attacks during prenylamine treatment was 1.7 and during placebo medication for a comparable period 2.5. The same patients took a daily average of 2.9 nitroglycerin tablets during prenylamine treatment and 3.7 tablets during comparable placebo periods. These results agree well with the over-all results obtained for Groups I and II and support their statistical evaluation.

Figs. 1 and 2 represent the combined means of the daily number of anginal attacks for each two-week interval of the trial including the initial single-blind dose titration part. The two graphs clearly demonstrate that the prenylamine effect is reproducible with each change in medication. A statistical comparison of the periods of the double-blind parts confirmed the visual demonstration. In all of the six possible combinations of adjacent medication periods in the two sequences of the double-blind part (N_1A_1, A_1N_2, N_2A_2 and A_1N_1, N_1A_2, A_2N) prenylamine reduced the number of attacks significantly except for the comparison N_1A_1. The decrease of *nitroglycerin consumption* during prenylamine administration was similarly reproducible with each change *in medication*.

The qualitative data entered by the patients on their report cards (severity of attacks, general well-being, walking distance) were also subjected to a statistical analysis using the sign test (Table IV). For each patient, a total of 144 possible comparisons is possible, because each of the twelve placebo weeks can be compared with each of the twelve prenylamine weeks. Thus it can be stated for each weekly comparison whether with placebo the severity of the attacks, for example, was the same as, or more, or less than with prenylamine. If

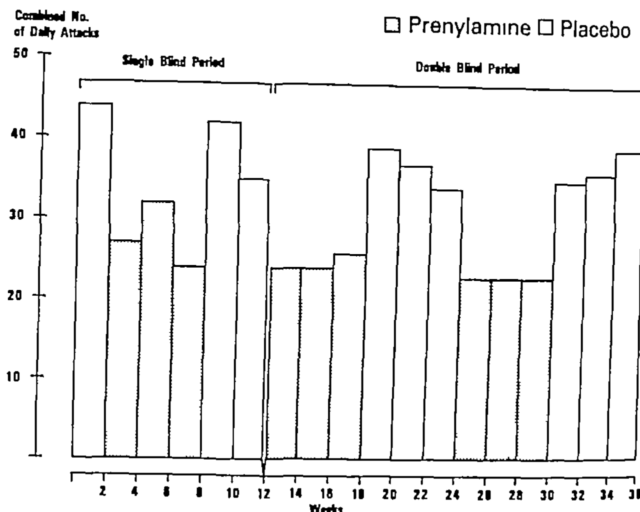


Fig 2 Combined daily number of anginal attacks in patients of Groups I and II (n = 24) during single-blind and double-blind period of trial Double-blind sequence

the sum of all weekly comparisons un favorable for prenylamine is smaller than that unfavorable for placebo the patient is considered a responder and counted in n and n+ in Table IV In the reverse case where the sum of all weekly comparisons unfavorable for prenylamine exceeds the sum of those unfavorable for placebo the patient is counted in n but not in n+ In case of equal sums the patient is not counted in either n or n+

The consistency of the data in Table IV is such that they could be summarized across the four groups and then be tested for significance with a simple sign test Obviously the difference between prenyl amine and placebo is highly significant re garding the severity of attacks weeks with no attacks and how the patient felt With respect to the walking distance the dif ference between placebo and prenylamine is not statistically significant

In a multiclinical trial it is necessary to check whether one or a few investigators could influence the outcome by studying more patients than the others. Moreover it had to be evaluated whether the results were affected by other variables such as the dosage age of patient history of myocardial infarction and concurrent diseases.

As shown in Table V none of the vari ables had an effect sufficient to justify the computation of a statistical test of signifi cance

The blood pressure did not differ to any noticeable degree during the various inter vals of the trial This observation agrees with earlier findings that therapeutic doses of prenylamine do not significantly affect blood pressure. In contrast the pulse rate was generally lower when the patients took prenylamine than during placebo periods (see Tables II and III) Fig 3 shows the mean pulse rates for nine patients of Groups I and II who began the double-blind part with placebo and wh rds

Table IV Statistical analysis (sign test) of qualitative variables†

Group	Sequence	Severity of attacks		Weeks with no attacks		How pt felt		Walking	
			n+		n+		n+		n+
I	$A_1N_1A_2N_2$	7	6	5	5	8	6	7	3
I	$N_1A_1N_2A_2$	9	7	5	5	8	6	5	3
II	$A_1N_1A_2N$	16	14	8	7	16	12	16	10
II	$N_1A_1N_2A_2$	8	6	4	3	9	5	9	3
Total		40	33	22	20	41	29	37	19
p‡		0 000		0 000		0 006		0 500	

*Twelve weeks of placebo and twelve weeks of prenylamine medication allow 144 comparisons for each patient and his answers to one of the three questions below. As judged by the totals of the number of comparisons of weeks, the comparison may be favorable or unfavorable for prenylamine in that patient. Equal totals are third possibility. If the result is in favor of prenylamine the patient is counted in both and n+. Should the result be in favor of placebo, the patient is counted in only. In case of equal totals the patient is not counted in either or +.
†The questions asked were the following:
Were anginal attacks more severe, same as usual, less severe?
In general, I felt better, same, worse.
I walked more, same, less.
‡p is the probability of obtaining n+ or more successes of independent trials of an experiment having two possible outcomes, each having probability of one half.

*Table V Effect of several variables on trial results**

1 *Age of patients (yr.)*	*40 or less*	*41 50*	*51-60*	*61-70*	*71 and over*	*Total*
No. of patients	2(2)	9(9)	8(8)	12(12)	12(12)	43(43)
No. of responders†	2(1)	7(6)	8(7)	10(10)	12(12)	39(36)

2. *Investigator‡*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*Total*
No. of patients	3(3)	2(2)	3(3)	7(7)	4(4)	9(9)	15(15)	43(43)
No. of responders	3(2)	2(2)	3(3)	7(7)	2(2)	9(9)	13(11)	39(36)

3 *N of prenylamine or placebo tablets per day*	*2*	*3*	*4*	*5*	*Total*
No. of patients	1(1)	24(24)	14(14)	4(4)	43(43)
No. of responders	1(1)	21(19)	13(12)	4(4)	39(36)

4. *Previous myocardial infarction*	*Yes*	*No*	*Total*
No. of patients	25(26)	18(17)	43(43)
No. of responders	23(22)	16(14)	39(36)

5 *No of concomitant diseases*	*1*	*2*	*3*	*4*	*5*	*Total*
No. of patients	18(18)	12(12)	8(8)	3(3)	2(2)	43(43)
No. of responders	16(14)	12(11)	7(7)	2(2)	2(2)	39(36)

*Figures without parentheses are based on number of anginal attacks per day; figures in parentheses are based on number of nitroglycerin tablets taken per day.
†Excluded from the number of patients are those who had the same number of anginal attacks in the prenylamine and placebo periods. Responders are those patients whose number of attacks (or nitroglycerin tablets) per day was less in prenylamine than in placebo periods.
‡Seven of the eight authors were the investigators responsible for the performance of the trial.

contained a complete series of measurements. For patients starting with prenylamine ten complete series were available and their means are shown in Fig 4

The resting and exercise ECG's were evaluated after the trial by one of the investigators without his knowledge at which period of the study they had been

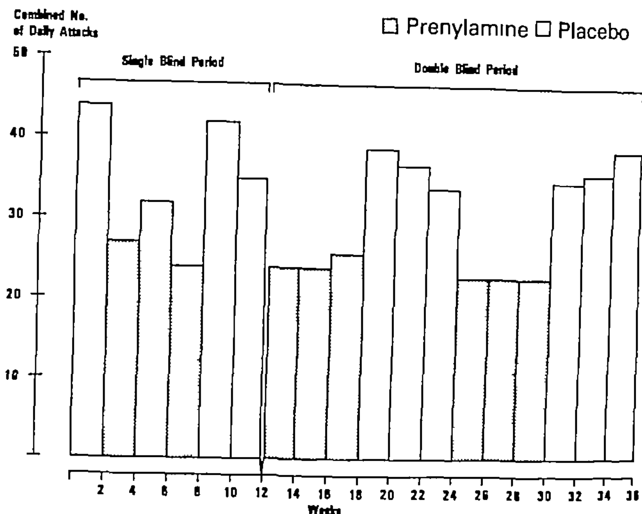


Fig. 2. Combined daily number of anginal attacks in patients of Groups I and II (n = 24) during single-blind and double-blind periods of trial. Double blind sequence A, $N_1A_2N_2$.

the sum of all weekly comparisons unfavorable for prenylamine is smaller than that unfavorable for placebo the patient is considered a responder and counted in n and n+ in Table IV. In the reverse case where the sum of all weekly comparisons unfavorable for prenylamine exceeds the sum of those unfavorable for placebo the patient is counted in n but not in n+. In case of equal sums the patient is not counted in either n or n+.

The consistency of the data in Table IV is such that they could be summarized across the four groups and then be tested for significance with a simple sign test. Obviously the difference between prenylamine and placebo is highly significant regarding the severity of attacks, weeks with no attacks, and how the patient felt. With respect to the walking distance the difference between placebo and prenylamine is not statistically significant.

In a multiclinical trial it is necessary to check whether one or a few investigators could influence the outcome by studying more patients than the others. Moreover it had to be evaluated whether the results were affected by other variables such as the dosage, age of patient, history of myocardial infarction, and concurrent diseases.

As shown in Table V none of the variables had an effect sufficient to justify the computation of a statistical test of significance.

The blood pressure did not differ to any noticeable degree during the various intervals of the trial. This observation agrees with earlier findings that therapeutic doses of prenylamine do not significantly affect blood pressure. In contrast the pulse rate was generally lower when the patients took prenylamine than during placebo periods (see Tables II and III). Fig. 3 shows the mean pulse rates for nine patients of Groups I and II who began the double blind part with placebo and whose records

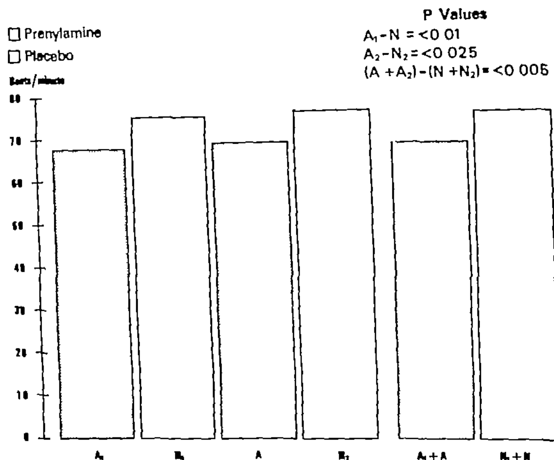


Fig. 4 Pulse rates for patients (= 10) during treatment with prenylamine (A) and placebo (N) Sequence A N₁A₂N

administration. Among a host of other side effects, more or less evenly distributed between prenylamine and placebo periods, one case of urticarial dermatitis is most likely attributable to the active drug because similar skin reactions have been reported in the literature.

Discussion

The combination of a single-blind part of 12 weeks with a double-blind double cross-over part of 24 weeks represents a very sensitive trial design for the evaluation of an antianginal drug In addition to allowing the effectiveness of the agent to be assessed over an extended period of time this design also lends itself well to investigating the reproducibility of the anti anginal action.

The close agreement between the number of anginal attacks at the beginning and at the end of the placebo sequences of the single-blind period of the trial demonstrates that the angina was stable and thus the main criterion for selecting patients fulfilled. The similarity in the antianginal effect of prenylamine during the single blind and the double-blind periods of the trial strongly supports the evidence for the reproducibility of that effect in a trial lasting as long as nine months.

Both in the single-blind and the double blind periods prenylamine reduced the number of anginal attacks by an average of about 30 per cent. This figure agrees well with the results of previous controlled studies with prenylamine.[-4] An examination of Tables II and III reveals, however that for the therapeutic success in an individual patient the 30 per cent figure has little meaning. There are patients whose response is excellent and reproducible,

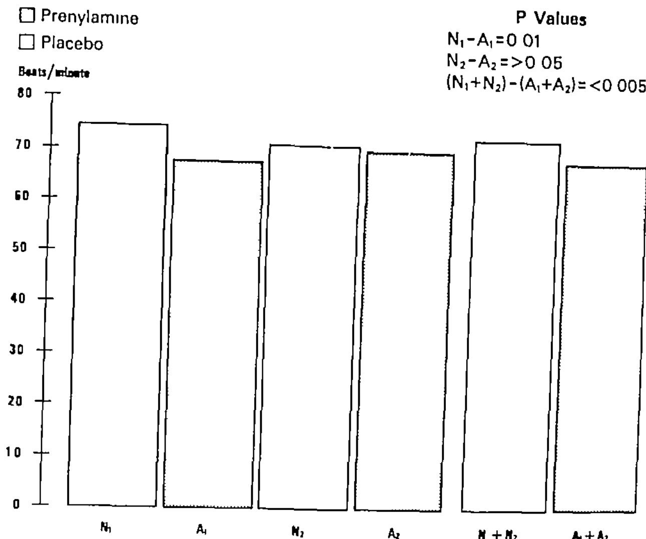


Fig 3 Pulse r tes for patie t (= 9) during treatment with prenylamine (A) and placebo (N) Sequence N A N A2.

recorded Subsequent assignment of the electrocardiographic records to the appropriate medication period did not reveal any distinct effect of prenylamine

Dropouts and side effects

Twenty-one patients did not complete the trial for a variety of reasons. Among these were three deaths. One patient died of cardiac arrest during the single-blind period in the initial two weeks of placebo administration a second patient died of myocardial infarction during the same period while he was taking prenylamine The third patient died suddenly of myocardial infarction during the placebo period of the double blind part of the trial

Of the remaining 18 patients nine terminated the study in the single-blind part and nine in the double-blind part. The reasons for discontinuation and the periods at which this occurred are listed in Table VI

In accordance with the clinical literature on prenylamine sedation was by far the most common side effect during the trial It was reported under a variety of descriptive terms, by 92 per cent of the patients when they took the active drug as compared to 67 per cent for the placebo periods. At various times but most often during the dose-titration part 36 per cent of the patients experienced the opposite effect nervousness or an allied symptom The corresponding figure for the placebo periods was 14 per cent. A high incidence of gastrointestinal reactions was reported for both the prenylamine and placebo periods Thus, episodes of nausea with or without vomiting occurred in 35 per cent of the patients while taking the active drug but also in 22 per cent during placebo

A negative inotropic effect and a reduction of the effect of isoproterenol on myocardial contractility and cardiac rate has been observed only in animal experiments with high doses of prenylamine.[11] In the absence of corresponding findings in man given prenylamine at therapeutic doses, it is unlikely that the antianginal effect of prenylamine is due to decreased myocardial contractility and oxygen consumption.

In isolated preparations and following its intravenous administration in man and dogs, prenylamine increases coronary blood flow probably by a direct action on the vascular muscle,[11,14] but this effect is assumed to be negligible on oral administration.

As judged by the rather extensive literature, the most interesting property of prenylamine is its catecholamine-depleting effect.[illegible] No direct evidence for this effect is thus far available for man. Several investigations, however, obtained indirect evidence by showing that the daily oral administration of 180 mg. of prenylamine for five days produced a significant decrease of the effect of intravenously infused tyramine on blood pressure and cardiac rate.[illegible] This decrease implies a prenylamine-induced catecholamine depletion since the tyramine effect is due to the release of norepinephrine and thus depends on the catecholamine amount available in the storage granules.

Additional findings are available which suggest a general attenuating effect of prenylamine on the adrenergic system. In patients undergoing emotional stress or exercise the administration of prenylamine at therapeutic doses caused a decrease of vanillylmandelic acid and catecholamine excretion.[illegible] At the same time, the rise in blood pressure and cardiac rate following exercise was significantly less than in normal controls.[14]

It is, therefore, conceivable that prenylamine diminishes the release of the adrenergic transmitter in emotion- or exercise-induced activation of the sympathetic nervous system. Among the various hypothetical explanations for the mechanism of the antianginal effect of prenylamine, its attenuation of the adrenergic action on the heart seems at present the most likely one. Furthermore, it agrees well with the significant reduction of the cardiac rate observed during the trial.

Summary

The effectiveness of prenylamine in reducing the frequency and severity of anginal attacks was evaluated in office patients selected by seven investigators. The trial lasted 36 weeks. The initial 12 weeks were done in a single-blind manner and six of these weeks were used to establish the maximal well tolerated dose of prenylamine for each patient. Placebo was given both before and after the dose-titration period. During the next 24 weeks, the trial was carried out as a double-blind double cross-over study. The patient had to enter the daily number of anginal attacks and nitroglycerin tablets taken into a report card. He was also requested to fill in the answers about the severity of the attacks, how he felt, and the distance he was able to walk.

Of the 69 patients who started the trial 48 completed it. Four of the complete records could not be used.

The most common side effects during the trial were, in order of their frequency, sedation, gastrointestinal intolerance, and nervousness. However, all of these symptoms also occurred during the placebo medication. Three patients died during the trial, two others about one month after they had discontinued it. No relationship between the cause of death and prenylamine is apparent. One case of urticarial dermatitis is most likely attributable to the drug.

The statistical analysis by the Wilcoxon matched-pair signed-rank test showed that the number of anginal attacks and nitroglycerin consumption were significantly less during prenylamine than during placebo sequences. The reproducibility of the effect of prenylamine in the double cross-over design was excellent.

Qualitative information regarding the severity of the anginal attacks and how the patients felt showed that the patients clearly benefited during prenylamine administration.

The statistical analysis of most of the results of the trial was carried out by Stanford Research Institute, Menlo Park, Calif.

Table VI Reasons for discontinuation of trial

Reason for discontinuation	*No of patients*			
	Single-blind part		*Double-blind part*	
	Prenylamine	*Placebo*	*Prenylamine*	*Placebo*
Death (myocardial infarction, 2 cardiac arrest 1)	1	1		1
Hospitalization (senile dementia 1 probable myocardial infarction 1 orthopedic problem 1)	1			2
Wanted coronary artery surgery				2
Acute pulmonary edema	1			
Progressive heart failure			1†	
Skin rash	1‡		1	
Nausea (and vomiting)	2	1		
Tiredness	2		1	
Unknown		1		2

Patient died of congestive heart failure about one month after discontinuation.
†Deterioration noted earlier in last placebo period of single-blind part.
‡Patient died about one month after discontinuation of acute myocardial infarction. Skin rash had also appeared during placebo medication.

whereas others respond only moderately well or not at all The response does not seem to depend on the severity of the angina nor is it related to the dose of prenylamine (see Table V) Furthermore patients with a previous myocardial infarction responded as well as those without a history of such an event

The reduction of the number of anginal attacks and nitroglycerin consumption is only a part although the most important one of the over all therapeutic efficacy of prenylamine Of interest is also the effect of the drug on the severity of the attacks, and on general condition of the patient The statistical analysis (Table IV) demonstrates a significant decrease in the severity of the attacks, which further supports the effectiveness of prenylamine. Expectedly the number of weeks with no attacks was significantly greater for prenylamine than for placebo The significant improvement of the general condition of the patients as indicated by the answers to how they felt, again supports the positive results.

Physical activity represented by the distance the patient walked did not differ significantly during placebo and prenylamine periods. This would imply that prenylamine did not improve the patient's capability for physical activity However more important for the validity of the trial is the conclusion that physical activity was not reduced because of the obvious sedative effect of prenylamine The reduced number of attacks can thus not be attributed to general inactivity of the patients because of sedation

The mode of action by which prenylamine reduces the frequency and severity of anginal attacks has thus far eluded a satisfactory explanation

A reduction of the cardiac rate which is desirable in angina pectoris, occurred in 37 of 43 patients during the trial Mean reduction was about 9 per cent but in individual patients cardiac rate decreased by as much as 25 per cent. A relationship between the degree of prenylamine induced bradycardia and the decrease in the number of anginal attacks was not apparent Patients whose angina was not improved by prenylamine showed as little or as much reduction of their pulse rates as those who responded excellently to the drug It must, however be considered that measuring the pulse rates in office patients once at two-week intervals is insufficiently exact to find out whether the frequency of attacks is quantitatively related to cardiac rate.

Experimental and laboratory reports

Influence of hemorrhage on the QRS complex of the electrocardiogram

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The effect of hemorrhage on the QRS complex, the RS-T interval, and the T wave of the electrocardiogram (ECG) has been reviewed by Lepeschkin[1] in man as well as in experimental animals. The changes in the amplitude of the QRS complex in experimental animals are reportedly produced by hypoxia, changes in lung volume, or rotation of the heart. The purpose of the present study was to investigate in cats whether these mechanisms or others are responsible for the QRS decrease during hemorrhage.

Methods and materials

The experiments were carried out in adult male and female cats. Anesthesia was induced by 25 to 40 mg. per kilogram of intraperitoneal sodium thiopentone. Cannulae were introduced into the trachea, both femoral arteries, and the femoral vein. In some of the cats the influence of the clamping of the vena cava was tested. After opening of the abdominal wall, the vena cava ligatures were carried out between the liver and the diaphragm. Heart catheters (No. 10 gauge) were introduced into the left ventricle through the carotid artery for the purpose of pressure measurements and additional filling of the ventricle with physiologic saline solution. In some cats the pericardium was firmly fixed to the chest. This was accomplished by cutting the rib cage next to the sternum and separating it with a retractor. The cat was artificially respirated by a Howard respiratory pump (Model 670). The intact pericardium was fixed to the side of the open chest by silk sutures.

Standard ECG Leads I, II, III, aVR, aVL, and aVF, precordial Leads V_1 to V_6 and V_{3R} to V_{6R}, as well as the scalar tracings X, Y, and Z were recorded with the use of a Grass (Model 7) six-channel polygraph.

Comparative experiments were done in intact dogs, guinea pigs, rats, and mice.

Results

During the removal of 16 to 26 c.c. per kilogram of body weight of blood from the femoral artery of both intact cats and those

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Prenylamine lactate (Segontin®) was supplied by Hoechst Pharmaceutical Company Cincinnati Ohio.

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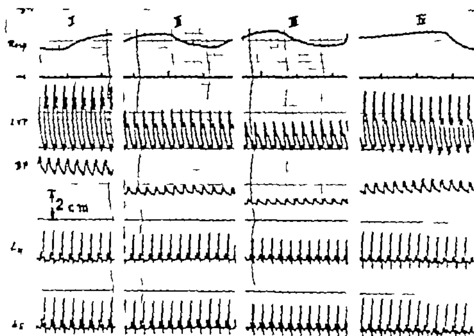


Fig. 2. ECG recordings from Leads L_{II} and L_I before hemorrhage (*I*) during hemorrhage of 7 c.c. blood per kilogram of body weight (*II*) and 16 c.c. blood per kilogram of body weight (*III*) and after stopping of hemorrhage without replacement of blood (*IV*). *Resp.*, respiration. *L.V.P.* left ventricle pressure measured by heart catheter. *B.P.* blood pressure. The 2 cm. calibration is 100 mm. Hg, or 1 mv. ECG amplitude.

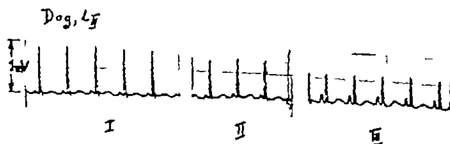


Fig. 3. ECG recording of Lead L_I in dog, before bleeding (*I*) during bleeding (after removal of 10 c.c. blood per kilogram of body weight (*II*) and after removal of 21 c.c. blood per kilogram of body weight (*III*).

or when they were given insufficient artificial ventilation after the administration of Scoline (succinylcholine) no reduction occurred in the amplitude of the QRS complex. However the ECG changes usually seen during anoxia were present, such as depression of the S-T segment.

When cardiac filling was diminished by clamping the vena cava between the liver and the diaphragm the amplitude of the QRS complex was again reduced simultaneously with the fall in blood pressure. Release of the clamp restored the blood pressure, and the QRS complex gradually returned to normal (Fig. 5). Conversely when the normally functioning left ventricle was overfilled by intracardial perfusion of 0.5 to 1 c.c. saline per second the QRS complex increased in amplitude temporarily (Fig. 6).

Discussion

Lepeschkin in his review of the influence of acute hemorrhage on the ECG of laboratory animals, summarizes that the voltage of the QRS especially that of R, decreases, and that the QRS axis usually deviates to the right these changes in the ECG resemble those seen in hypoxia and were attributed by him to an increase in

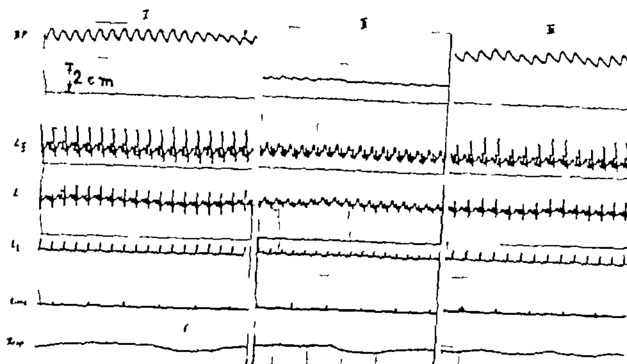


Fig. 1. ECG recordings from Leads L_I, L_{II}, and L_{III} in a sodium thiopentone anesthetized cat taken before bleeding (I), during bleeding of 16 c.c. blood per kilogram of body weight (II), and after replacement of the blood (III). Blood pressure (B.P.) readings were 225/175 (period I), 70/60 (period II), and 200/150 (period III). The 2 cm. calibration is 100 mm. Hg, or 1 mv. ECG amplitude. Time is marked in seconds. Resp, respiration.

with open chests, a reduction in the amplitude of the QRS complex occurred, observed in all three standard limb leads. Those animals which showed opposite patterns in different leads during bleeding were not taken into account, as in these cases positional changes of the heart due to the bleeding could not be excluded. The reduction in the amplitude of the QRS complex occurred without a change in its duration and before any alteration in heart rate took place. The T wave was not depressed or inverted but was sometimes enlarged in all three leads (Fig. 1, I and II).

In order to exclude the possible influence of change of heart position during the hemorrhage, experiments were carried out in which the pericardium was firmly fixed to the chest wall by silk sutures. Under these conditions as well, bleeding caused decrease of the QRS amplitude.

The changes in the QRS amplitude occurred immediately after removal of less than 7 c.c. per kilogram body weight of blood and were clearly marked after removal of 16 to 26 c.c. per kilogram of body weight. Blood analysis during this period revealed no change in the hematocrit and hemoglobin concentrations.

In some experiments when the hemorrhage was stopped, the initial fall in blood pressure was followed by a slight rise accompanied by an increase in the amplitude of the R wave toward normal (Fig. 2). There were also associated changes in P, Q, S, and T waves.

When the removed blood or the equivalent volume of saline was replaced immediately after hemorrhage, the amplitude of the QRS increased back to its original height during the infusion. The replacement of fluid was always carried out before any reflex increase in blood pressure occurred (Fig. 1, III).

The reduction in the QRS amplitude observed in the cat was also confirmed in the dog after removal of 25 per cent of the blood volume (Fig. 3); it was confirmed as well in guinea pigs, rats, and mice.

In some experiments the ECG was recorded with unipolar chest leads V_1 to V_6 and V_{3R} to V_{6R}, in addition to the three limb leads. The reduction in the amplitude of the QRS complex occurred in each of the chest leads. Some of the changes are shown in Fig. 4. Recordings were also made from the scalar tracings X, Y, and Z.

When the cats inhaled CO_2-enriched air

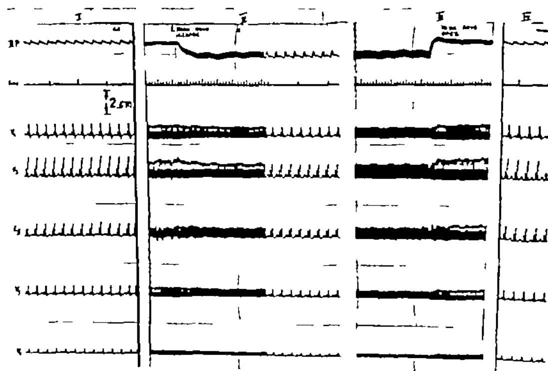


Fig. 5 ECG recordings from precordial Leads V V V and V and from limb Lead L_4 before clamping of the inferior vena cava (*I*), during clamping (*II*) during opening of the vena cava clamp (*III*) and after opening (*IV*). The 2 cm. calibration is 100 mm. Hg, or 1 mv ECG amplitude.

obtained after surgical fixation of the heart in a given position throughout a number of experiments. Thus QRS changes due to bleeding were obtained without position changes of the heart.

In the experiments in which hemoglobin concentrations (%Hgb) and hematocrit were measured no change was found during the period of QRS amplitude decrease. Changes in % Hgb and hematocrit were observed only after a longer period of time had elapsed from the start of blood removal and after stronger bleeding

It appears therefore that the real cause for the decrease in QRS amplitude after bleeding must be found in the reduced heart volume, which might lead to changes mechanoelectric transduction n the cardiac muscle. The following experimental evidence is relevant.

When the vena cava was clamped without hemorrhage produced diminished heart filling and consequently diminished heart volume the QRS amplitude reacted exactly as in the case of hemorrhage. Conversely release of the vena cava clamp was followed by immediate normalization of the R potential as was the case when blood or saline were returned into circulation after previous bleeding Overfilling of the left ventricle, obtained by intracardial infusion of saline (1 c.c. per second) produced an expected increase of the QRS amplitude which also returned to normal after cessation of the procedure.

Two questions arise from this hypothesis —first, whether the phenomenon of the QRS amplitude decrease occurs in man as well as in mammalian experimental animals, and second whether the reduced heart volume produces changes in the electrical phenomena of the heart. As to the first question QRS amplitude decrease has been observed repeatedly during sudden surgical blood loss (Gassner unpublished report) and infusion of blood or saline restores the QRS to normal Such observations have not been made outside the operating theater[8,9] since in cases such as traumatic hemorrhage, for example, clinical measures as transfusion of blood or other liquids are started immediately to interrupt

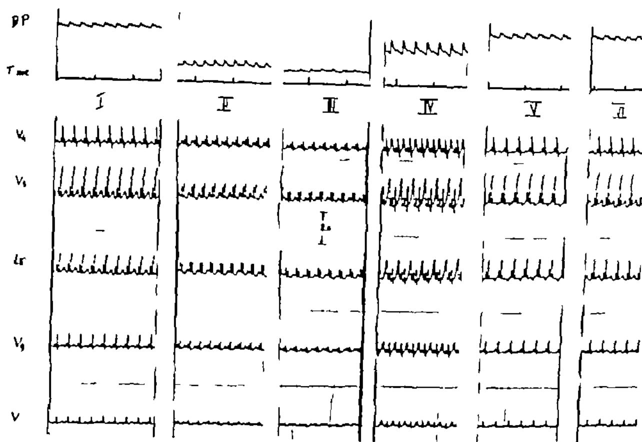


Fig. 4. ECG recordings from precordial Leads V[illegible], V$_2$, V$_6$, and V$_1$ and from limb Lead L_{II} before bleeding (*I*) during bleeding of 10 c.c. blood per kilogram of body weight (*II*) and 16 c.c. blood per kilogram of body weight (*III*) during replacement of 10 c.c. blood per kilogram of body weight (*IV*) immediately after replacement of 16 c.c. blood per kilogram of body weight (*V*) and some time later (*VI*). *B.P.* blood pressure. The 2 cm. calibration is 100 mm. Hg, or 1 mv. ECG amplitude.

lung volume and rotation of the heart due to dilatation. Other authors have not described such change in the QRS in association with hemorrhage but examination of some of their records reveals that such a reduction in the amplitude of the QRS wave did in fact occur.[3] Reduction in the QRS complex in man is known to appear in secondary anemia,[3] certain cardiomyopathies,[4,5] and pericarditis.[6]

In the present study the influences of hypoxia, increased lung volume, and rotation of the heart were evaluated. In regard to hypoxia the results of our experiments show that the QRS amplitude does not decrease during prolonged apnea or during CO_2-enriched air breathing and in some experiments it even increases. Furthermore, the phenomenon of decrease in the QRS amplitude occurs immediately at the induction of and during hemorrhage and disappears gradually under the influence of compensatory regulating mechanisms brought into action by the hemorrhage. Hypoxia has not yet developed at the time when the QRS change occurs, evidenced also by the unchanged S-T interval and normal T wave in the ECG.

The possible influence of lung volume changes can be eliminated as a cause of the QRS changes as lung volume was kept constant throughout by executing the experiments under artificial respiration started even before bleeding had been induced.

With regard to the possible influence on the QRS amplitude of rotation of the heart due to hemorrhage, the ECG recordings were carefully controlled and only those experiments were considered in which no rotation occurred. This involved recordings of the standard leads of aV_R, aV_L, and aV_F, the precordial Leads V_1 to V_6 and V_{3R} to V_{6R} as well as the scalar tracings of X, Y, and Z. Even in the complete absence of position changes of the heart, QRS amplitude decrease was registered during bleeding. QRS amplitude decrease after bleeding was also

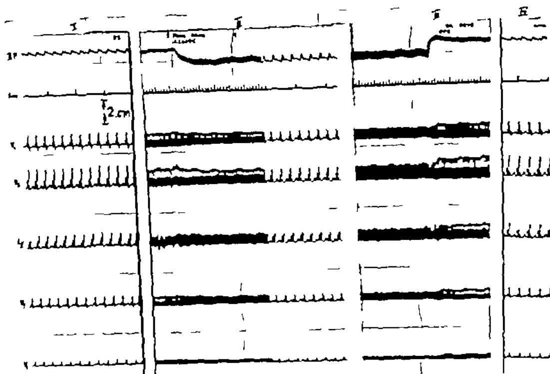


Fig. 5. ECG recordings from precordial Leads V V V and V and from limb Lead L_{II} before clamping of the inferior vena cava (*I*) during clamping (*II*) during opening of the vena cava clamp (*III*) and after opening (*IV*). The 2 cm. calibration is 100 mm. Hg, or 1 mv. ECG amplitude.

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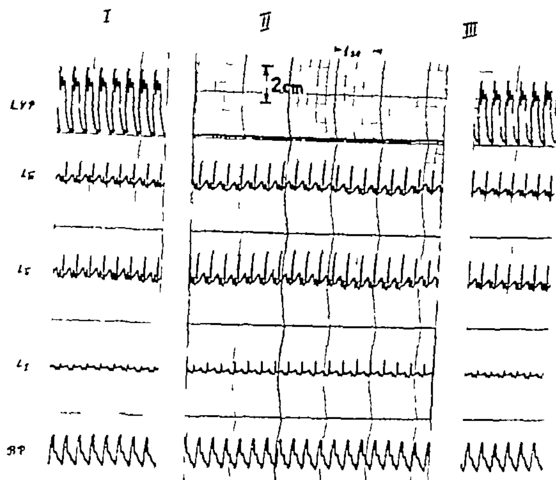


Fig. 6. ECG recordings from limb Leads L_I, L_{II}, and L_{III} before overfilling of the left ventricle (*I*), during overfilling of 0.3 c.c. per kilogram of body weight per second (*II*), and after stopping of overfilling (*III*).

the bleeding before ECG recordings are made. Furthermore, QRS reduction has been reported in certain diseases such as pericarditis. One could again assume that constriction of the heart produced by pericarditis is responsible.

With regard to the second question, studies are presently underway on the changes produced in the electrical phenomena of the heart and their possible significance as a feedback mechanism regulating heart function according to heart filling.

Summary

The removal of blood from anesthetized cats or dogs invariably produces an immediate reduction of the amplitude of the QRS complex which can be restored to normal by reinjecting the blood. In the present study it was demonstrated that the QRS changes are directly related to the changes of the heart volume, viz., reduction of QRS amplitude after bleeding or after clamping of the inferior vena cava or increase after overfilling of the heart. Anoxia, changes of lung volume, or rotation of the heart had not contributed to the registered QRS changes.

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The effect of diphenylhydantoin sodium (Dilantin) on myocardial contractility and hemodynamics

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The antiarrhythmic effects of Dilantin have been demonstrated in both animals and man. In 1950, Harris and Kokernot[1] showed that Dilantin abolished ventricular arrhythmias following experimental myocardial infarction. The drug was also effective against arrhythmias induced by digitalis, aconitine, and hypothermia.[2-4] The electrophysiologic studies by Helfant and associates[5] and others[6-9] have shown that Dilantin depresses ventricular automaticity without a significant prolongation of intraventricular conduction time. In addition, it accelerates atrioventricular conduction. These investigators have also reported that Dilantin protects against the electrophysiologic effects of digitalis excess without altering its inotropic response. Clinical studies reviewed elsewhere[10, 11] suggest that Dilantin is useful in digitalis-induced arrhythmias, especially ventricular ectopic beats. Arrhythmias of short duration such as those following anesthesia, surgery, cardiac catheterization, cardioversion, and so on, have been effectively treated with Dilantin.[10] On the other hand, Dilantin is ineffective against atrial fibrillation, flutter, and sinus tachycardia.

While the electrophysiologic studies suggest that Dilantin may be superior to quinidine and procainamide, fatalities which have been reported following its clinical use have been attributed to a precipitate decline in cardiac function.[12, 13] Studies on the hemodynamic effects of Dilantin indicate that it causes a variable fall in cardiac output and arterial pressure, these effects being related to the dose and rate of administration of the drug.[14-16]

The present investigation was undertaken to study the effects of Dilantin on cardiac contractility as defined by myocardial force-velocity relation. The velocity of shortening was measured by means of a strain gauge assembly described previously.[17, 18] In addition, the effects of the drug on circulatory hemodynamics were examined.

Methods

Experimental studies were performed on 30 mongrel dogs weighing 15 to 22 kilograms and anesthetized with 25 mg. per kilogram of pentobarbital given intravenously. The trachea was intubated and artificial ventilation with room air was instituted by means of a Harvard respirator pump. Left ventricular and aortic pressures were monitored by means of No. 8 Fr. stiff catheters, directly connected to

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Statham P23 DB strain-gauge systems. Zero level for pressure measurements was set at the midchest position. The first derivative of the left ventricular pressure pulse (dp/dt) was obtained by means of an R-C differentiating circuit. Left ventricular end-diastolic pressure (LVEDP) was recorded using higher sensitivity at the end-expiratory phase of the respiratory cycle. Cardiac outputs were determined from the indicator dilution curves obtained by injecting indocyanine green dye into the right atrium and sampling continuously from the ascending aorta by means of a Harvard withdrawal pump and a Gilford Densitometer.

An intracardiac strain-gauge catheter assembly described previously in a series of publications was[17] used to register curves of fiber shortening in 15 of the experiments. Briefly, the device consists of two strain gauge bearing prongs mounted on a flexible stylet which is threaded through an intracardiac catheter. With the catheter positioned suitably against the ventricular wall the prongs are projected from the catheter and engaged into the ventricular wall. As the prongs follow the course of fiber shortening in systole, curves of fiber shortening are inscribed on a beat-to-beat basis. From the simulatneously recorded curves of fiber shortening and pressure pulse, instantaneous force-velocity relations were determined at an isolength point according to the method described previously.[7] All events were recorded optically on an Electronics for Medicine recorder. Dilantin was administered intravenously as 5 mg. per kilogram in 18 experiments, in six of which velocity of shortening was measured (Group I). In 12 experiments, in six of which velocity of shortening was measured, Dilantin was administered as 10 mg. per kilogram (Group II). In both groups of experiments the drug was diluted in 10 ml. of saline and given slowly over a period of five minutes. In addition, effects of an undiluted bolus injection of Dilantin (10 mg. per kilogram) were also studied in three experiments. The maximum effect of the drug was seen within the first one to two minutes after completion of the injection. The data recorded at this time were utilized for statistical analysis. Repeated recordings were made at 5, 10, and 15 to 20 minutes after injection of the drug. Recovery of cardiac dynamics was evident at 5 minutes and was nearly complete by 15 to 20 minutes. Calculations of tension time index (T.T.I.) and peripheral vascular resistance (PVR) were made according to the methods reported previously.[20]

Results

Myocardial force-velocity relation. As shown in Fig. 1, both the force and velocity of shortening declined after Dilantin ($p < 0.01$); the instantaneous force-velocity relation determined at an isolength point thereby shifted downwards and to the left indicating a diminution in myocardial contractile state. This effect was transient and lasted up to five minutes, after which progressive recovery occurred. A greater decline in velocity of shortening occurred when the dose of Dilantin was increased from 5 to 10 mg. per kilogram (Tables I and II) but the difference was not significant; the fall in force of contraction was, however, significantly greater with the increase in dosage of Dilantin. When Dilantin was given undiluted in a single bolus of 10 mg. per kilogram, the curve of fiber shortening became flat. This was accompanied by a precipitate fall in left ventricular systolic pressure (average of 90 mm. Hg) and a marked rise of left ventricular end-diastolic pressure (average of 8.0 mm. Hg). This hypodynamic state of left ventricle lasted from three to five minutes, after which gradual recovery occurred in 15 to 20 minutes.

Hemodynamics. In Group I, Dilantin was administered in a dose of 5 mg. per kilogram (Table I, Figs. 2, 3, and 4). The left ventricular systolic pressure fell by 28.6 ± 2 mm. Hg and the mean arterial pressure fell by 26.6 ± 2.8 mm. Hg. The rate of left ventricular pressure rise (dp/dt) showed a fall of 927 ± 119 mm. Hg/sec. while the tension time index (T.T.I.) fell by 315 ± 8 mm. Hg/sec./min. The peripheral vascular resistance (PVR) dropped by 1,010 ± 240 dynes/sec./cm^{-5}. The decline in all of these parameters was statistically significant ($p < 0.005$). The left ventricular end-diastolic pressure (LVEDP) showed an increase of 2.2 ± 0.4 mm. Hg ($p < 0.001$)

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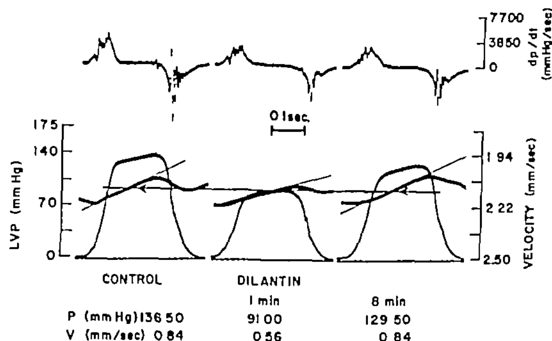


Fig 1 Effect of Dilantin on myocardial force velocity relation. At an isolength point (indicated by arrows) velocity of shortening (V) was derived by drawing a tangent to the curve of shortening relating height of deflection to time. Left ventricular pressure related in time to the isolength point indicated force (P) Dilantin resulted in a decrease in velocity of shortening and force of contraction pointing to a depression of myocardial contractility Recovery is shown to occur at 8 minutes after the drug was injected

The heart rate varied It increased in eight of the animals fell in three and remained unchanged in one the average change was $+7 \pm 3$ beats per minute The stroke volume and cardiac output also varied The stroke volume rose in six of the animals and fell in the remaining six the average change being $0\ 3 \pm 0\ 8$ ml The cardiac output increased in eight of the animals and fell in six the average change being 247 ± 121 ml per minute (Table I) The average change in heart rate stroke volume and cardiac output was not significant

In Group II where Dilantin was given in a dose of 10 mg per kilogram the effects of the drug were more marked than in Group I (Table II Figs. 2 3 and 4) Thus the left ventricular systolic pressure fell by $75\ 8 \pm 5\ 7$ mm Hg ($p < 0\ 001$) and the mean arterial pressure by 69 ± 6 mm Hg ($p < 0\ 001$) LV dp/dt showed a fall of $2\ 436 \pm 299$ mm Hg/sec ($p < 0\ 001$) and T T I fell by $2\ 052 \pm 306$ mm Hg/sec./min ($p < 0\ 001$) The peripheral resistance showed a fall of $1\ 739 \pm 469$ dynes/sec/cm^{-5} ($p < 0\ 001$) while LVEDP rose by $2 \pm 0\ 4$ mm Hg ($p < 0\ 005$) Slowing of the heart rate was seen in all of the animals ($12 \pm 4\ 5$ beats per minute $p < 0\ 05$) The stroke volume rose in four of the animals and fell in two the average change being $0\ 5 \pm 1\ 2$ ml The cardiac output on the other hand fell in four of the animals and rose in two the average change being -75 ± 242 ml per minute

A comparison of Groups I and II (Table II Figs 2 3 and 4) shows that there was a significantly greater fall ($p < 0\ 001$) in left ventricular systolic pressure mean arterial pressure T T I and dp/dt in Group II than in Group I Peripheral vascular resistance also fell more in Group II than in Group I The fall in heart rate was more consistent in Group II which is in contrast to the variable changes observed in Group I On the other hand there was no difference in the changes in stroke volume observed in the two groups. Because of the greater fall in heart rate in Group II cardiac output fell more frequently than in Group I

Discussion

A negative inotropic action of Dilantin is shown by the downward and leftward shift in myocardial force-velocity relation (Fig 1) The decline in velocity of shortening as an index of depressed myocardial

Table I Group I Hemodynamic effects of Dilantin (5 mg per kilogram)

	Control	Dilantin (5 mg./Kg.)	Change: Mean ± S.E.	Change: Significance (P)
LVP (mm. Hg)*	158 9	130 3	−28 6 ± 2	< 0 001
Velocity of shortening (mm./sec.)	1 025	0 500	−0 525 ± 0 085	< 0 001
LVEDP (mm. Hg)	4 4	6 8	2 2 ± 0 56	< 0 001
MAP (mm. Hg)	135	108 4	−26 6 ± 2 8	< 0 001
dp/dt (mm. Hg/sec.)	5 397	4 470	−927 ± 119	< 0 001
T T I (mm. Hg/sec./min.)	3 127	2 812	−315 ± 89	< 0 005
PVR (dynes/sec./cm.⁻⁵)	4 230	3 220	−1 010 ± 240	< 0 005
Heart rate (beats/min.)	157	164	7 ± 3	NS
SV (ml.)	18 4	18 7	0 3 ± 0 8	NS
CO (ml./min.)	2 860	3 107	247 ± 121	NS

*LVP = Left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; MAP = mean arterial pressure; dp/dt = maximum rate of left ventricular pressure rise; T.T.I. = tension time index; PVR = peripheral vascular resistance; SV = stroke volume; CO = cardiac output; SE = standard error; NS = not significant.

Table II Group II Hemodynamic effects of Dilantin (10 mg per kilogram)

	Control	Dilantin (10 mg./Kg.)	Change: Mean ± S.E.	Change: Significance (P)	Significance of difference between Groups I and II (P)
LVP (mm. Hg)	220	144 2	−75 8 ± 5 7	< 0 001	< 0 001
Velocity of shortening (mm./sec.)	1 025	0 471	−0 50 ± 0 049	< 0 001	NS
LVEDP (mm. Hg)	6 8	8 8	2 ± 0 4	< 0 005	NS
MAP (mm. Hg)	186	117	−69 ± 6	< 0 001	< 0 001
dp/dt (mm. Hg/sec.)	6 314	3 878	−2 436 ± 299	< 0 001	< 0 001
T T I (mm. Hg/sec./min.)	5 507	3 455	−2 052 ± 306	< 0 001	< 0 001
PVR (dynes/sec./cm.⁻⁵)	4 442	2 703	−1 739 ± 469	< 0 001	NS
Heart rate (beats/min.)	165	153	−12 ± 4 5	< 0 05	NS
SV (ml.)	21 6	22 1	0 5 ± 1 2	NS	NS
CO (ml./min.)	3 488	3 413	−75 ± 242	NS	NS

Abbreviations same as in Table I.

contractile state becomes even more significant in view of the marked fall in left ventricular afterload and a rise in left ventricular end-diastolic pressure (Tables I and II) both of which factors favor an increase in velocity of shortening.[7,21,23]

It was shown previously[11,13] that a simultaneous recording of the curves of fiber shortening and ventricular pressure pulse before and after an intervention can be used to identify changes in myocardial contractile state. By selecting an isolength point at a time in systole when the rate of ventricular pressure change is zero the effects of series elastic can be minimized[17,21] so that the velocity of fiber shortening can be equated with the velocity of shortening of the contractile elements. An inverse relation between force and velocity characterizes the properties of contractile elements.[21] A decline in velocity of shortening despite of a fall in LV afterload therefore, points to a direct depression of the myocardial contractile state by Dilantin.

Depression of myocardial contractility was also reflected in the fall of LV dp/dt

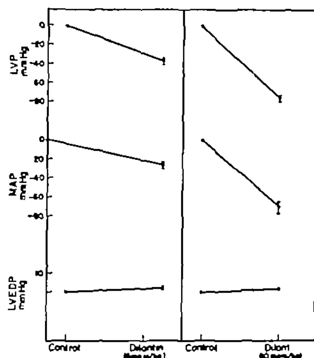


Fig 2 Hemodynamic effects of Dilantin A greater fall in left ventricular systolic pressure (LVP) and mean arterial pressure (MAP) occurred when the dose of Dilantin was increased from 5 to 10 mg per kilogram. The increase in left ventricular end-diastolic pressure (LVEDP) was not different.

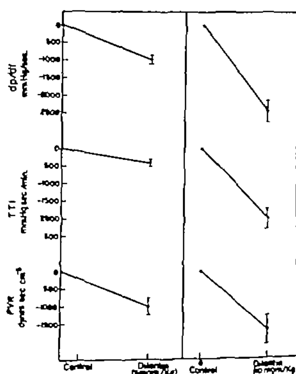


Fig 3 Hemodynamic effects of Dilantin. A significant fall in dp/dt, T T I and PVR occurred after Dilantin the fall was greater with 10 as compared to 5 mg per kilogram of the drug (abbreviations as in Table I)

which occurred despite a rise in LVEDP (Fig 3) The rate of left ventricular pressure rise (dp/dt) is principally determined by the end-diastolic fiber length afterload and myocardial contractile state[21,22] The marked fall in left ventricular afterload accounts for some of the fall in LV dp dt however the design of the present study does not permit differentiation of the role of this factor from that of the depressed contractile state Mixtar and associates[16] and Vasko and associates[13] reported significant fall in LV dp/dt after Dilantin

The fall in left ventricular afterload observed after Dilantin was quite striking this effect became more marked as the dose of the drug was increased (Fig 3 Table II) This was best reflected in the changes in T T I (Fig 3) The fall in LV systolic pressure mean arterial pressure and peripheral resistance was also marked (Figs 2 and 3) Since the cardiac output did not change significantly the decline in peripheral resistance seems to be due to peripheral vasodilation Vasodilatory effects of Dilantin have been reported by Vasko and associates[13] Mixtar and associates[16] and Gupta and associates.[14] Gupta and associates[14] also showed a marked increase in coronary blood flow due to direct vasodilation of coronary arteries by Dilantin In studies by Mixtar and colleagues[16] vasodilation persisted despite cardiovascular denervation indicating that the drug acted directly on peripheral blood vessels.

In spite of depressed myocardial contractility stroke output did not fall significantly after Dilantin (Fig 4) This finding is similar to the reported changes in cardiac index in man[24,25] Changes in stroke volume may be explained by the opposing effects of depressed contractility and fall in peripheral resistance on stroke output A fall in peripheral vascular resistance and hence aortic impedance facilitates ventricular ejection this factor may partly counteract the effects of depressed contractility on stroke output.

The principal effect of an increase in the dose of Dilantin from 5 to 10 mg per kilogram was in the form of a significantly greater fall in left ventricular afterload (Table II) This was reflected in T T I mean arterial pressure and calculated peripheral resistance On the other hand the change in velocity of shortening stroke

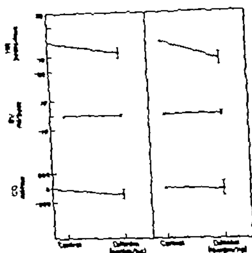


Fig. 4 Hemodynamic effects of Dilantin. The average changes in stroke volume and cardiac output was not significant with either dose of Dilantin. Heart rate fell more consistently with 10 than with 5 mg. per kilogram of the drug.

volume, and cardiac output was not significantly different (Tables I and II).

Several investigators have reported varying hemodynamic effects of Dilantin in man. Lieberson and colleagues[26] found that in patients with heart disease Dilantin resulted in a decrease in stroke work and stroke power whereas LVEDP showed an increase. Average cardiac index was, however not significantly changed. Conn and colleagues[27] found no significant changes in cardiac output and peripheral vascular resistance. Childress and colleagues[28] reported a *fall* in arterial pressure and a rise in LVEDP whereas cardiac index was unchanged. Therapeutic use of Dilantin has occasionally resulted in a severe and even fatal depression of cardiac function.[29-31] This has usually occurred when the drug was administered rapidly in large and undiluted amounts. This condition was duplicated in the present study by rapid intravenous injection of undiluted Dilantin in a dose of 10 mg. per kilogram. A severe although short lasting depression of myocardial contractility occurred as shown by flattening of the *curve of fiber shortening* and a precipitate *fall* of LV systolic pressure. Such severe depression of myocardial contractility even if of short duration is potentially hazardous in patients, especially if the cardiac function is previously impaired.

Summary

Dilantin when administered intravenously diluted in saline resulted in a downward and leftward shift of the myocardial force-velocity relation indicating depression of the myocardial contractile state. A marked fall in LV dp/dt tension time index and peripheral vascular resistance also occurred. As a result of the opposing effects of depressed myocardial contractility and fall in peripheral resistance on ventricular ejection, fall in stroke volume and cardiac output was not significant.

An increase in the dose of Dilantin from 5 to 10 mg. per kilogram resulted in a significantly greater fall in LV afterload whereas the changes in velocity of shortening and stroke output were not significantly different. When Dilantin was *injected* undiluted as a bolus, the curve of fiber shortening became flat there was a precipitate fall in LV systolic pressure, and a marked rise of LVEDP indicating hypodynamic myocardial failure.

These effects of Dilantin lasted from three to five minutes and a complete recovery was evident in 15 to 20 minutes.

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Effects of dipyridamole on myocardial clearance of Rb^{86} and on some parameters of central hemodynamics in man without coronary arterial disease

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As a potential agent for the treatment of coronary arterial disease in man dipyridamole (D) has evoked great interest. Studies in dogs with the use of different techniques, have shown that intravenous administration of the drug is followed by a significant and prolonged increase in coronary blood flow. Similar effects have been shown in man[1-4] and coronary arteriographic studies have demonstrated an increase in diameter of the coronary vessels with enhanced opacification of the finer tributaries.[5-11] Long term oral administration of D to dogs undergoing occlusion of a coronary artery produced a significant increase in their survival.[12] In other studies, animals treated with D and subjected to occlusion of a coronary artery exhibited a substantial proliferation of the satellite anastomotic network in comparison with control animals.[13-16] Clinical evaluation of this drug, however, has been to some extent conflicting. On the one hand a considerable body of published evidence attests to generally favorable therapeutic experience with D;[17] on the other hand, well-controlled double-blind studies have shown no significant difference between D and a placebo in the short term management of angina pectoris or acute myocardial infarction or in the prevention of electrocardiogram (ECG) alterations in exercise tests.[18-21] These controversial observations have led some authors to suggest that the increase of coronary blood flow under the influence of D may not be accompanied by a corresponding increase of myocardial perfusion, the latter representing that fraction of coronary blood flow involved in metabolic exchanges at the cellular level.[22] The investigation which is the subject of this report was, therefore, designed to evaluate the effect of the drug on an index of myocardial perfusion, i.e., myocardial Rb^{86} clearance (MC Rb), with simultaneous measurements of main pulmonary and systemic hemodynamic variables by means of radiocardiography. In this way it was hoped to define more conclusively the acute effects of intravenous D in man.

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*The commercial name of the drug used is Persantin.

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onds (*MPCTsec.*) Mean pulmonary circulation time in seconds equals (right peak time to left peak time) + (right peak time to commencement of left peak)/2.

Mean pulmonary circulation time in systoles (*MPCTsyst*) Mean pulmonary circulation time equals

$$\frac{\text{MPCTsec.}}{60/F}$$

Stroke volume (*SV*) Stroke volume equals

$$\frac{CO}{F}$$

Pulmonary blood volume (*PBV/sq.M*) Pulmonary blood volume equals SV × MPCTsyst./body surface area in square meters.

Total blood volume (*TBV/sq M*) Total blood volume equals

$$\frac{D}{c\ eq}/\text{body surface area in square meters.}$$

Mean arterial pressure (*MAP*) Mean arterial pressure equals diastolic pressure + 1/3 pulse pressure.

Peripheral resistance (*PR*) Peripheral resistance equals

$$\frac{1332 \times \text{MAP(mm Hg)}}{\text{CO(ml./sec.)}} \text{dynes/sec.}^{-}/\text{cm.}^{-5}$$

External work of the left ventricle (*LVW*) External work of the left ventricle equals

$$\frac{\text{CO(1/min.)} \times \text{MAP(mm. Hg)} \times 13.6}{1\,000} \text{Kg M./min}$$

In addition to statistical analyses of the data from all 25 subjects, the data from each subgroup were examined With the use of the base-line readings as control for each subject, the Student t test was applied to obtain the probability values and level of significance Figs. 1 to 6 show the changes in the main variables for each individual patient together with the mean change and the level of statistical significance.

Results

Effects 3 minutes after intravenous injection of 10 mg. of D Five out of the 6 treated subjects exhibited an increase of MC Rb while no change was observed in the last one. The average increase was from a base-line value of 107 7 to 125.5 ml per minute per 100 Gm (+16.5 per cent) This increase is statistically significant ($p < 0.01$) Although increases in CO heart rate stroke volume and left ventricular work were also found these were not of statistical significance neither were the observed decreases in mean arterial pressure and peripheral resistance (Figs. 1 to 6)

Effects 3 minutes after intravenous injection of 20 mg. of D In all the subjects an increase of MC Rb was observed The mean increment was from a control level of 115 1 to 155 1 ml per minute per 100 Gm. (+34 7 per cent $p < 0.01$) The other indices showed significant changes as follows CO +31 9 per cent, $p < 0.01$ heart rate +22.8 per cent, $p < 0.05$ stroke volume, +11 9 per cent, $p < 0.15$ pulmonary blood volume +13 7 per cent $p < 0.05$ left ventricular work, +28.2 per cent, $p < 0.025$ mean arterial pressure, −2 1 per cent $p < 0.05$ and peripheral resistance, −22.8 per cent $p < 0.025$ (Figs 1 to 6)

Effects 10 minutes after intravenous injection of 20 mg. of D MC Rb was increased in 10 subjects a slight reduction was observed in the other 2. The mean increase was from a control value of 114 6 to 137.3 ml per minute per 100 Gm (+19.8 per cent, $p < 0.012$) Significant changes in other variables were as follows CO +9 8 per cent, $p < 0.005$ heart rate, +6.2 per cent $p < 0.05$ stroke volume +3.5 per cent $p < 0.025$ total blood volume, +3.8 per cent $p < 0.05$ left ventricular work +8 4 per cent, $p < 0.005$ and peripheral resistance, −9.3 per cent, $p < 0.005$ The slight reduction of mean arterial pressure did not reach significance, and pulmonary blood volume in contrast with the above quoted results showed a slight fall without statistical significance (Figs. 1 to 6)

Over-all analysis showed an average increase of MC Rb from a control level of 113 1 to 139.5 ml per minute per 100 Gm (+23.3 per cent, $p < 0.001$) Other significant changes were as follows CO +16 1 per cent, $p < 0.002$ heart rate +8 per cent $p < 0.01$ stroke volume +7 0 per cent, $p < 0.05$ total blood volume, +6 5

Methods

Myocardial clearance of Rb^{86} and other radiocardiographic data were measured according to the method of Donato and associates.[22, 23] This technique requires rapid injection into the right atrium of a single radioactive bolus containing 200 μc of Rb^{86} and 50 μc of I^{131}-labeled albumin (RISHA). During the first 30 seconds after injection selective precordial recordings are made of the time radioactivity curves for the two isotopes. Precordial counting is performed from 30 to 90 seconds after injection during the same period blood is drawn from the brachial artery for measurement of radioactivity concentration Five minutes after injection when the RISHA concentration has reached equilibrium precordial and blood radioactivity are again measured

Investigations were carried out in the morning on fasting patients in a supine position without premedication A catheter (Deseret Intracath No 1914) was introduced percutaneously via the basilic vein to the superior caval vein or right atrium The brachial artery was cannulated with a Cournand needle Precordial radioactivity was monitored by a 2 × 2 inch NaI Tl scintillation counter provided with a cylindrical collimator 6 cm in diameter and 12 cm in length Under radiologic control this was set at the level of the left ventricle and connected to a digital recording system (Picker Multiprober and Texas Instrument Company recorder) Precordial curves were recorded with a time constant of 0 5 second and a selective recording for the two isotopes was obtained by simultaneous use of two channels with analyser setting of 310 to 390 kilo electron volts (KEV) for RISHA and of 760 to 2 000 KEV for Rb^{86} Under these conditions the contribution of RISHA to the counting rate of the Rb^{86} channel was zero whereas the contribution of Rb^{86} to the counting rate of the RISHA channel was approximately 25 per cent which was subtracted in later calculations The position of the collimator over the chest wall of the patient remained constant throughout the investigation Blood radioactivity was measured in a well counter under the same conditions as for precordial counting Brachial artery pressure was recorded externally at the same time as determinations of MC Rb and cardiac output (CO) were carried out

Twenty men and 5 women between the ages of 19 and 69 years (average age, 38 years) were studied None exhibited evidence of cardiovascular disease After base line evaluation D was injected intravenously over a period of 3 minutes In the first group of 6 subjects a dose of 10 mg was given while the second group of 7 subjects received a 20 mg dose In all 13 subjects the evaluation technique was repeated immediately after administration of the drug Twelve further subjects received a dose of 20 mg and evaluation was delayed until 10 minutes after administration In accordance with the original authors, calculation of the various parameters was then carried out as follows

Myocardial clearance of Rb^{86} *(MC Rb)*

This value is given by the ratio $\frac{Rm}{A\ Rb}$

where Rm is the myocardial component of a precordial counting rate measured from 30 to 90 seconds after injection of the tracer (Rb^{86}) This parameter is obtained by subtracting the intracavity and intravascular component from the total radioactivity A Rb is the area of first Rb circulation in the cardiac chambers recorded at precordium[22]

Cardiac output (CO) Cardiac output equals

$$\frac{d \times 120}{A\ RISHA} \times \frac{a\ l\ eq}{c\ eq} \times 0\ 83$$

where d equals the dose of injected RISHA A RISHA is the area of first circulation of RISHA in the cardiac chambers recorded at precordium a l eq equals the average level per dt of precordial radioactivity at equilibrium (RISHA) c.eq equals the blood radioactivity concentration per milliliter at equilibrium (RISHA) 120 equals the factor for conversion into minutes of selected dt of 0 5 second and 0 83 equals heart fraction i e the fraction of precordial counting rate at equilibrium attributable to cardiac and vascular components contributing to the radiocardiographic curve.[24, 25]

Heart rate (F)

Mean pulmonary circulation time in sec

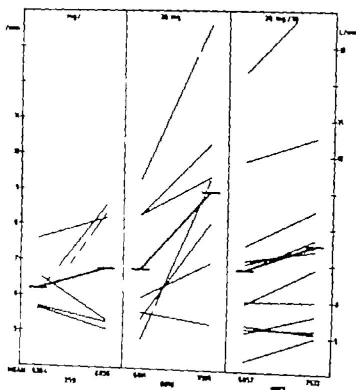


Fig. 2. Changes in cardiac output after dipyridamole.

Fig. 3. Changes in left ventricular work after dipyridamole.

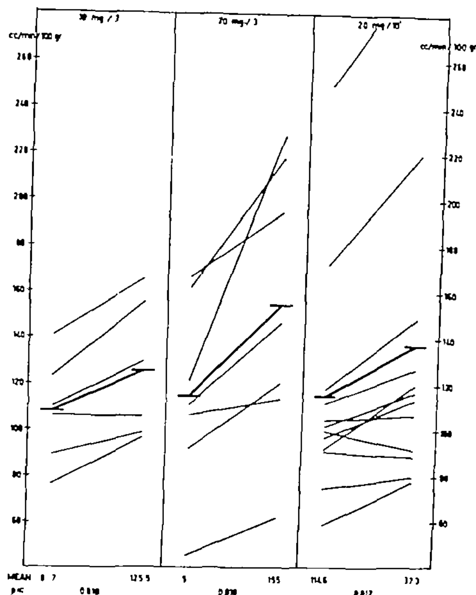


Fig *1* Changes in myocardial clearance of Rb[86] after administration of dipyridamole the three groups of subjects examined Light lines represent single cases heavy lines represent the mean values.

per cent $p < 0.002$ left ventricular work $+14.1$ per cent $p < 0.002$ mean arterial pressure -2.0 per cent $p < 0.002$ and peripheral resistance -12.7 per cent $p < 0.002$ Changes in pulmonary blood volume and in mean pulmonary circulation time in systoles were not significant.

Discussion

An increase of MC Rb has been found in 22 out of 25 subjects examined A mean increase of 16 5 per cent was apparent 3 minutes after intravenous injection of 10 mg of *D* in 6 subjects *Under the same* conditions, a dose of 20 mg resulted in a mean increase of 34 7 per cent in 7 subjects. After the latter dose a mean increase of 19 8 per cent was still evident 10 minutes after administration (Fig 1)

These observations accord well with the findings of other authors who have used different techniques. Thus in dogs a maximum increase of coronary blood flow occurs a few minutes after intravenous injection of *D* [1,3,4,6] *The present study however* indicates that under the influence of D the increase of coronary blood flow is associated with improved perfusion of myocardial *tissue* since *the technique used* which is based upon myocardial extraction

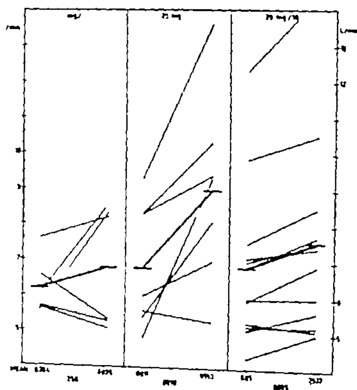


Fig Changes in cardiac output after dipyridamole.

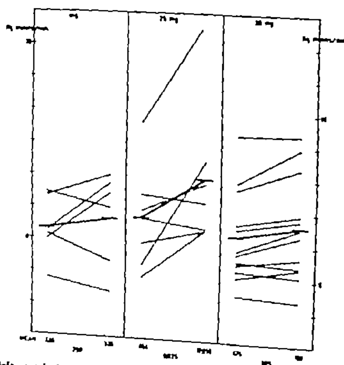


Fig. 3 Changes in left ventricular ork after dipyridamole.

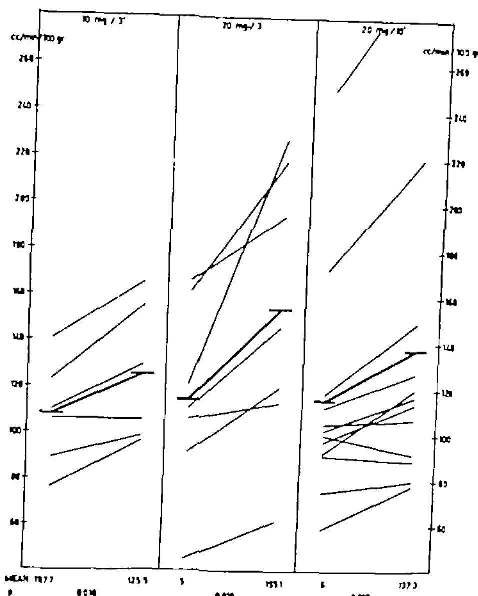


Fig. 1. Changes in myocardial clearance of Rb^{86} after administration of dipyridamole in the three groups of subjects examined. Light lines represent single cases, heavy lines represent the mean values.

per cent, $p < 0.002$; left ventricular work, $+14.1$ per cent, $p < 0.002$; mean arterial pressure, -2.0 per cent, $p < 0.002$; and peripheral resistance, -12.7 per cent, $p < 0.002$. Changes in pulmonary blood volume and in mean pulmonary circulation time in systoles were not significant.

Discussion

An increase of MC Rb has been found in *22 out of 25 subjects examined. A mean* increase of 16.5 per cent was apparent 3 minutes after intravenous injection of 10 mg of *D in 6 subjects. Under the same* conditions, a dose of 20 mg resulted in a mean increase of *34.7* per cent in *7* subjects. After the latter dose a mean increase of 19.8 per cent was still evident 10 minutes *after administration (Fig. 1).*

These observations accord well with the findings of other authors who have used different techniques. Thus in dogs a maximum increase of coronary blood flow occurs a few minutes after intravenous injection of D.[1,2,3,4] The present study, however, *indicates that under the influence of* D the increase of coronary blood flow is associated with improved perfusion of myocardial tissue since the technique used, which is based upon myocardial extraction

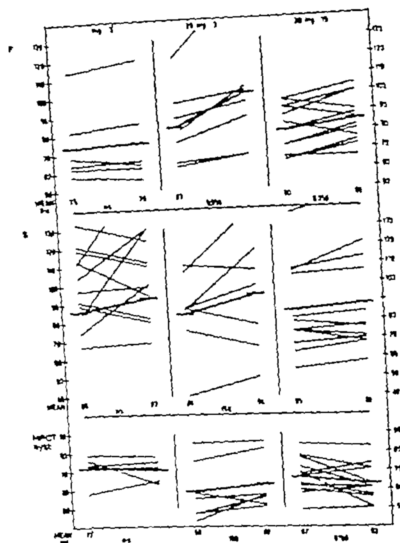


Fig. 6. Changes in frequency, stroke volume, and mean pulmonary circulation time after dipyridamole. The level of significance is also given (n.s. = not significant).

of a radioactive tracer from the circulation allows estimation of that fraction of coronary blood flow involved in metabolic exchanges at the cellular level.

The discrepancies between clinical and experimental reports,[11-17] together with the observation that the oxygen saturation of the blood drawn from the coronary sinus has constantly been found to increase after D,[7] prompted some authors to suggest that D may increase coronary blood flow without concomitant enhancement of myocardial capillary perfusion.[31] The findings in the present study, however, directly contradict such an assumption. The evaluation of the hemodynamic effects of D has indicated a rise in CO with a related increase in left ventricular work. It is notable that these changes occurred concurrently with a reduction of peripheral resistance and mean arterial pressure.

Other investigators have found no changes or even a reduction of CO.[3,4,5,6,27] Some of these apparent discrepancies can be explained by differences in dosage. Furthermore, it should be emphasized that in these studies simultaneous determinations of coronary blood flow and CO were not undertaken, the latter being carried out after a lapse of time[3,4,6] when, according to the present data, the CO changes tend to disappear. It is also important to point out

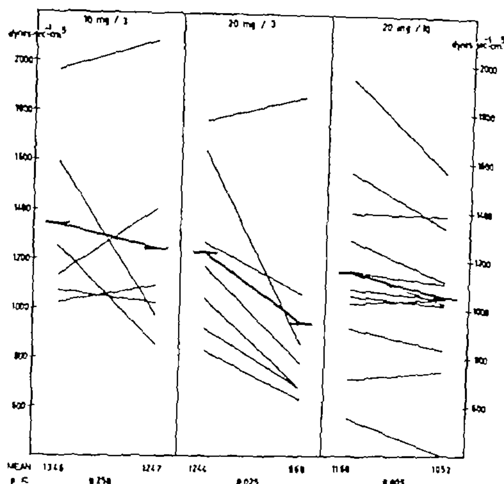


Fig. 4. Changes in peripheral resistance after dipyridamole.

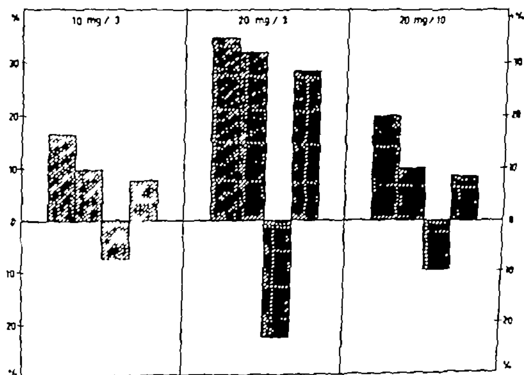


Fig. 5. Mean percentage changes of myocardial clearance (first bar), cardiac output (second bar), peripheral resistance (third bar) and left ventricular work (fourth bar) for each group of subjects examined.

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that in most cases these experiments were carried out on the anesthetized dog and the technique required the removal of a considerable volume of blood for the determination of coronary blood flow.[2,3,4] Data may be found in the literature which support our observation. Thus at doses within therapeutic range D exerts a direct positive inotropic action[28] *and produces a slight* increase in heart rate.[1,2,4,5,27] Only at higher doses as sometimes used in dogs a negative inotropic effect has been reported.[28] Furthermore in the dog if a constant CO is maintained D causes a marked fall in arterial pressure.[4] At therapeutic doses in man D rarely causes more than minimal reduction in arterial pressure; marked hypotension has not been reported. These findings are not only compatible with but even *suggest an increase of cardiac output. It is* important to stress however that the increase of CO and left ventricular work is always *less* pronounced and of shorter duration than the increase in MC Rb (Figs. 2, 3, and 4).

As shown in Fig. 5, 10 minutes after intravenous administration of 20 mg. of D a 19.8 per cent increase in MC Rb can still be found while CO and left ventricular work are proportionally much closer to basal values (Fig. 5).

The increase in CO under the influence of D is generally associated with increased *stroke volume.* However in the groups of subjects receiving a 20 mg. dose of the drug the increase in stroke volume has clearly *been complemented by a rise in heart rate* (Fig. 6).

Changes in pulmonary blood volume were not significant *although estimations* carried out immediately after the administration of the drug showed an increase in this parameter and later measurements showed a slight mean reduction. One possible explanation of this finding is that concomitant with the maximum increase of CO increased perfusion occurred in these areas of the pulmonary vascular tree which are usually incompletely perfused and the volume of which is systematically undervalued with dilution techniques. The same reasoning can be applied to explain the increase of total blood volume although it may also be argued that these changes could occur as a consequence of the widespread vasodilatation caused by D.

Summary

The hemodynamic effects of dipyridamole were evaluated in 25 subjects without evidence of coronary arterial disease. The method used involved estimation of myocardial Rb^{86} clearance with simultaneous recording of radiocardiographic data. In this way changes in myocardial perfusion due to the drug could be interpreted together with concurrent hemodynamic *changes in the systemic and pulmonary* circulation.

Dipyridamole was administered as a single intravenous dose of 10 mg. to 6 subjects and 20 mg. to 7 subjects. Determinations were made both before and 3 minutes after administration. In another 12 subjects determinations were made before and 10 minutes after an intravenous dose of 20 mg.

Dipyridamole produced a marked increase of myocardial clearance in the majority of these subjects. Three minutes after injection the observed increase of myocardial clearance was associated with an increase of cardiac output and left ventricular work and a reduction of peripheral resistance. Ten minutes after injection the effect on the coronary circulation was still present while the other changes tended to disappear. Thus the best relationship between myocardial perfusion and cardiac work was found 10 minutes after the administration of the drug.

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correlation between the accumulation of MDF and the low splanchnic blood flow that follows coronary embolization.

Methods

Animals Healthy mongrel dogs of either sex (mean body weight of 20.4 kilograms) were anesthetized with sodium pentobarbital (25 mg per kilogram of body weight) given intravenously. The trachea was intubated and the animal artificially ventilated with 100 per cent O_2 with the use of a Harvard piston respirator and an in-line CO absorber. The left common carotid and left jugular vein were cannulated and 20 ml per kilogram of body weight of Ringer's lactate solution with 5 per cent dextrose were given intravenously in order to assure adequate hydration prior to embolization. A splenectomy was performed, and an electromagnetic blood flow transducer was positioned around the origin of the superior mesenteric artery. A thoracotomy was performed through the left fourth intercostal space. An electromagnetic blood flow transducer was positioned around the root of the aorta, and the left atrium was cannulated. Mean arterial blood pressure (MABP), central venous pressure (CVP), and left atrial pressure (LAP) as an index of left ventricular filling pressure were measured with the use of Statham P 23 pressure transducers. Cardiac output (CO) and superior mesenteric artery flow (SMAF) were recorded by a Biotronix Laboratory pulsed-logic flowmeter. In addition, a Lead II electrocardiogram (ECG) was recorded. All cardiovascular variables were continuously monitored by means of a Honeywell 2106 Visicorder.

Hemodynamic calculations Superior mesenteric artery resistance (SMAR) and total peripheral resistance (TPR) were calculated by the formulas

$$SMAR = \frac{(MABP - CVP)}{SMAF}$$

and

$$TPR = \frac{(MABP - CVP)}{CO}$$

and were expressed in arbitrary peripheral resistance units (PRU). Left ventricular minute work (LVMW) was calculated by the formula

$$LVMW = (MABP - LAP) \times (CO)$$

Heart rate (HR) was taken directly from the ECG recording.

Embolization procedure Embolization was achieved by the injection of metallic mercury (1 ml per kilogram of heart weight) into the circumflex branch of the left coronary artery[9] under direct visualization. The criteria used to validate the occurrence of cardiogenic shock were the following: (1) a 40 per cent decrease in MABP, (2) a 40 per cent decrease in CO, and (3) ECG changes indicating infarction, namely, S-T segment elevation and broadening of the T wave. If cardiogenic shock was not induced within 15 minutes, an additional 0.05 ml of mercury was injected until the animal (1) exhibited cardiogenic shock, (2) fibrillated irreversibly or (3) failed to meet the shock criteria. If either of th last two phenomena occurred the animal was discarded from the study. Of the ten animals studied one dog fibrillated and one dog did not meet the criteria for cardiogenic shock. In addition five dogs were subjected to a sham cardiogenic shock procedure in which all the surgical procedures carried out in the cardiogenic shock animals were performed but the mercury was not injected. At the end of all surgical procedures (0 time) and 5 hours later arterial blood samples (25 to 35 ml) were collected for determination of plasma MDF activity.

Chemical determinations Samples of arterial blood (5 ml) were collected in cold heparinized syringes for determination of plasma β-glucuronidase and cathepsin activity at 0, 1, 3, and 5 hours following embolization or sham embolization. β-Glucuronidase activity of plasma samples was determined according to the method of Talalay, Fishman and Huggins[9] with the use of phenolphthalein glucuronide as substrate. β-Glucuronidase-specific activity was expressed as the number of micrograms of phenolphthalein released per milligram of plasma protein per hour at 37° C.

The method of Anson[10] was employed for the determination of plasma cathepsin activity using bovine hemoglobin as substrate. Specific activities for cathepsin were

Production of a myocardial depressant factor in cardiogenic shock

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The development of circulatory shock following myocardial infarction (cardiogenic shock) is a condition characterized by hypotension and a low cardiac output Twenty per cent of all patients with myocardial infarcts develop cardiogenic shock and the mortality rate for these patients with cardiogenic shock is 80 per cent [1]

The pathogenesis of cardiogenic shock is not well established nor are the therapeutic measures used in the treatment of this condition A failure to understand the pathophysiologic changes which occur in shock following myocardial infarction has hampered the development of a rational therapeutic approach

A myocardial depressant factor (MDF)[2] has been found in the plasma of animals in a variety of shock states including hemorrhagic shock endotoxin shock bowel ischemia shock and pancreatitis. MDF is a small peptide (molecular weight, 800 to 1 000)[3] which has been found to exert a prominent negative inotropic effect on the isolated papillary muscle [4] isolated perfused heart [5] and the *in situ heart.*[6] Recently MDF has been isolated from the plasma of clinical patients exhibiting various forms of shock including that induced by septicemia, bowel ischemia, and pancreatitis.[7] Lefer[2] has shown that MDF or its precursors may arise from the ischemic splanchnic region The initiating event appears to be the release of proteolytic enzymes from disrupted splanchnic lysosomes. These enzymes presumably participate in the formation of MDF by the cleavage of small peptides from proteins (i e either cellular or plasma proteins)

The primary aims of this investigation were (1) to determine whether lysosomal enzymes and MDF accumulate in the plasma during cardiogenic shock and if so (2) to determine whether there is a

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Table I. Hemodynamic status of dogs in cardiogenic shock

Variable	Sham shock, Group I (n = 5)	Shock Group II (n = 8)	Statistical significance*
MABP† (mm. Hg)			
0 hr	108 ± 6	106 ± 5	—
1 hr	113 ± 4	81 ± 7	< 0.005
3 hr	112 ± 3	92 ± 3	< 0.005
5 hr	103 ± 2	87 ± 7	< 0.05
CO (ml./min./Kg.)			
0 hr	105.2 ± 7.4	108.9 ± 2.9	—
1 hr	102.4 ± 5.1	54.6 ± 7.8	< 0.001
3 hr	93.8 ± 6.4	51.8 ± 7.3	< 0.001
5 hr	98.0 ± 10.0	50.0 ± 8.0	< 0.005
HR (beats/min.)			
0 hr	162 ± 10	138 ± 11	—
1 hr	164 ± 12	115 ± 10	< 0.05
3 hr	162 ± 11	119 ± 13	< 0.05
5 hr	160 ± 12	128 ± 15	—
LAP (mm. Hg)			
0 hr	6.0 ± 1.8	5.9 ± 0.9	—
1 hr	4.4 ± 1.2	6.8 ± 1.1	—
3 hr	5.2 ± 2.3	5.8 ± 1.1	—
5 hr	4.0 ± 2.2	5.9 ± 2.3	—
SMAF (ml./min./Kg.)			
0 hr	17.0 ± 1.5	16.5 ± 1.7	—
1 hr	16.1 ± 2.9	8.2 ± 1.1	< 0.005
3 hr	18.4 ± 2.3	6.6 ± 0.8	< 0.001
5 hr	20.0 ± 3.5	6.3 ± 0.1	< 0.005
SMAR (PRU)			
0 hr	5.9 ± 0.7	6.6 ± 0.8	—
1 hr	7.4 ± 1.2	10.3 ± 1.8	—
3 hr	6.3 ± 1.0	15.6 ± 3.8	< 0.05
5 hr	5.6 ± 1.0	15.3 ± 3.0	< 0.02
TPR (PRU)			
0 hr	41.0 ± 5.2	47.7 ± 3.6	—
1 hr	45.9 ± 5.6	69.8 ± 6.3	< 0.01
3 hr	50.5 ± 6.2	91.3 ± 13.6	< 0.0[illegible]
5 hr	45.7 ± 4.9	91.6 ± 10.2	< 0.005
LVMW $\frac{(\text{mm. Hg})\ (\text{L.})}{(\text{min.})}$			
0 hr	252.5 ± 26.4	218.7 ± 16.0	—
1 hr	261.7 ± 23.0	91.7 ± 18.4	< 0.001
3 hr	236.0 ± 13.1	86.8 ± 9.2	< 0.001
5 hr	223.7 ± 15.2	82.4 ± 15.2	< 0.001

*The p value refers to comparisons between Groups I and II at the same time. All values are means ± standard error of the mean (S.E.M.).

†Abbreviations: CO, cardiac output; CVP, central venous pressure; HR, heart rate; LAP, left atrial pressure; LVMW, left ventricular minute work; MABP, mean arterial blood pressure; SMAF, superior mesenteric artery flow; and SMAR, superior mesenteric resistance.

(60 per cent) occurred 60 minutes after coronary embolization and remained at this level over the next 4 hours.

The alterations in the hemodynamic status of Group II animals were effected in the postembolization survival times. Sham operated animals exhibited a survival time of 18.5 hours, whereas cardiogenic shock animals survived only 8.8 hours.

Previous studies have indicated that an inverse relationship exists between plasma

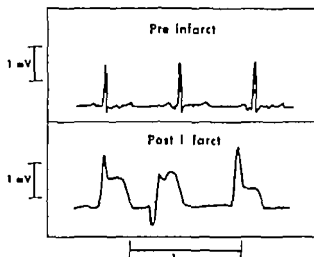


Fig. 1. Typical tracings of Lead II of the ECG in a dog prior to and 15 minutes after coronary embolization. Voltage (1 mv.) and time (1 second) calibrations are shown. The preinfarct ECG is typical for anesthetized dogs receiving positive-pressure ventilation in the open-chest state. The small notch which appears during the S-T segment occasionally occurs and may be an artifact of the open-chest state. The changes which occur after coronary embolization are quite dramatic. Essentially, a large elevation in the S-T segment occurs with prolonged ventricular repolarization. Frequent premature ventricular systoles are also observed (see second beat).

expressed as the number of milliequivalents of tyrosine released per milligram of protein per hour at 37° C.

Protein determinations were carried out employing a microbiuret technique with the absorbance read at 300 nanometers and calibrated with micro-Kjeldahl determinations.

Processing of plasma for MDF activity. Arterial blood samples (25 to 35 ml.) obtained at 0 time and 5 hours after embolization or sham embolization were centrifuged at 2,200 × g for 15 minutes and the plasma removed. The plasma was placed in Nojax dialysis tubing at 4° C. and 220 mm. Hg pressure for 24 to 36 hours. The protein-free ultrafiltrate obtained has been shown to contain all the MDF activity of whole plasma.[11] A 10 ml. aliquot of the ultrafiltrate was then lyophilized to dryness, reconstituted to 2 ml., applied to a Bio-Gel P-2 column, and eluted with Krebs-Henseleit solution according to previously described techniques.[8] The column fractionated the ultrafiltrate into six peaks, one of which, Peak D, contained all the MDF activity present in whole plasma. Peak D eluates were then assayed for MDF activity on isolated cat papillary muscles according to previously described techniques.[11] MDF activity was expressed in MDF units, 1 MDF unit being equal to a 1 per cent decrease in the developed tension of the isolated cat papillary muscle compared with Krebs-Henseleit solution as a standard.

Results

ECG changes following embolization are shown in Fig. 1. A typical tracing obtained in the postembolization period shows marked deviation of the S-T segment and a broadening of the T wave with no significant change in heart rate. Qualitative changes similar to these were observed in all eight animals of the cardiogenic shock group. None of the sham cardiogenic shock dogs exhibited these ECG abnormalities. The dogs which were injected with mercury exhibited a 43 per cent decrease in MABP from the postthoracotomy value of 120 ± 5 to 69 ± 5 mm. Hg 15 to 20 minutes after embolization. Similarly, cardiac output declined 49 per cent over the same period (from 109 ± 3 to 48 ± 6 ml. per minute per kilogram of body weight). Thus, all three criteria for the validation of cardiogenic shock were met.

A summary of the hemodynamic data obtained from dogs in sham cardiogenic shock (Group I) and dogs in cardiogenic shock (Group II) is shown in Table I. There are no significant differences between the animals of Groups I and II with regard to any of the zero hour hemodynamic values. MABP gradually decreased over the 5 hour postembolization period, reaching 77 per cent of control values at the end of this time. There was a 56 per cent fall in cardiac output in the first 10 to 15 minutes after embolization from 109 ± 3 to 48 ± 6 ml. per minute per kilogram of body weight. CO remained depressed over the remainder of the 5 hour postembolization period. The decreases in CO were accompanied by a 49 per cent decrease in SMAF within the first hour and a continual decline in SMAF over the next 4 hours. The decreases in CO and SMAF were associated with increases in TPR and SMAR, respectively, throughout the postembolization period. The peak decrease in LVMW

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3 hr	5.2 ± 2.3	5.8 ± 1.1	—
5 hr	4.0 ± 2.2	5.9 ± 2.3	—
SMAF (ml./min./kg.)			
0 hr	17.0 ± 1.5	16.5 ± 1.7	—
1 hr	16.1 ± 2.9	8.2 ± 1.1	< 0.05
3 hr	18.4 ± 2.3	6.6 ± 0.8	< 0.001
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5 hr	5.6 ± 1.0	15.3 ± 3.0	< 0.01
TPR (PRU)			
0 hr	41.0 ± 3.2	47.7 ± 3.6	—
1 hr	45.9 ± 3.6	69.8 ± 6.3	< 0.01
3 hr	50.5 ± 6.1	91.3 ± 13.6	< 0.01
5 hr	45.7 ± 4.9	91.6 ± 10.2	< 0.005
LVMW (mm. Hg) (L.)/(min.)			
0 hr	252.5 ± 26.4	218.7 ± 16.0	—
1 hr	261.7 ± 25.0	91.7 ± 18.4	< 0.001
3 hr	236.0 ± 13.1	86.8 ± 9.2	< 0.001
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*The p value refers to comparisons between Groups I and II at the same time. All values are mean ± standard error of the mean (S.E.M.).

†Abbreviations: CO, cardiac output; CVP, central venous pressure; HR, heart rate; LAP, left atrial pressure; LVMW, left ventricular muscle work; MABP, mean arterial blood pressure; SMAF, superior mesenteric artery flow; and SMAR, superior mesenteric resistance.

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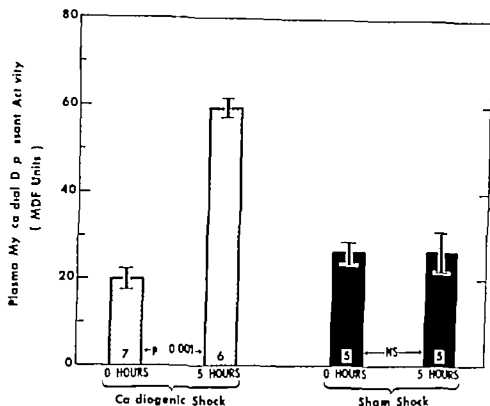


Fig. 2 Bar gr phs of plasma MDF activities in sham cardiogenic and cardiogenic shock animals, just prior to embolization (0 hours) and 5 hours after embolization. Height of the bars indicates mean MDF activity ex pressed n MDF u ts Bracket ndicate tand rd errors of the mean, and the n mbers in the bars indicate the number of animals used for MDF assay S gnificant MDF act vity occurred only in cardiogenic shock animals 5 hours after coronary embolization.

MDF activity and the survival of shock animals.[3] This relationship was also found to be present in this investigation Fig 2 summarizes the plasma MDF activities for Group I and Group II animals prior to embolization and 5 hours after emboliza tion There was a significant rise ($P < 0.001$) in the plasma MDF activity of dogs in cardiogenic shock 5 hours after emboli zation from 20 3 to 58 5 units. Conversely the plasma MDF activity of sham shock animals did not significantly increase over the 5 hour experimental period

The increases in plasma MDF activity of dogs in cardiogenic shock were associated with significant increases in the plasma activities for the lysosomal enzymes β-glu curonidase and cathepsin The activities for these enzymes prior to surgery and 4 hours after embolization or sham emboliza tion are shown in Table II Plasma lyso-somal enzymic activity did not significantly change during the surgical procedures, as evidenced by the fact that the operative and 0 hour (postoperative) values were essentially the same However 4 hours after embolization β-glucuronidase and cathepsin activities had doubled in the animals in cardiogenic shock The peak increases in specific activity of these en zymes occurred approximately 4 hours after embolization (i e 40 minutes after the maximum decrease in SMAF occurred) The increases in the plasma activities of these enzymes appear to reflect the severity of the splanchnic ischemia produced by embolization due to the decrease in SMAF

Discussion

The hemodynamic data obtained in this study support the work of others[8, 12, 14] who found that experimental cardiogenic shock is characterized by a low cardiac output and a relatively high total peripheral resistance In addition the fact that CO and LVMW did not increase in response to the activa tion of the sympathetic nervous system as evidenced by the increase in TPR indicates a continued deterioration of the myocar dium that may contribute to the lethality of the shock state

Little is known about the physiologic alterations which occur after myocardial infarction and their role in the pathogenesis

Table II. Plasma enzyme activities in cardiogenic shock

Time	β-Glucuronidase*		Cathepsin†	
	Sham	Shock	Sham	Shock
Preoperative	22.1 ± 4.4‡ (5)	21.3 ± 2.2 (5)	3.4 ± 0.8 (4)	3.0 ± 0.2 (4)
0 hr	18.7 ± 5.0 (5)	25.5 ± 3.0 (7)	2.7 ± 0.6 (5)	3.6 ± 0.6 (4)
4 hr	1.9 ± 2.5 (7)	45.8 ± 7.2 (6)	2.6 ± 0.5 (6)	7.0 ± 1.2 (7)

*β-Glucuronidase activities are expressed as micrograms of phenolphthalein $\times 10^{-3}$ released per milligram of plasma protein per hour at 37° C.
†Cathepsin activities are expressed as milliequivalents $\times 10^{-4}$ of tyrosine liberated per milligram of plasma protein per hour at 37° C.
‡All values are means ± S.E.M. Numbers in parentheses are the number of samples assayed.

of cardiogenic shock. Lillehei and associates[14] have attributed the shock state to a generalized peripheral vasoconstriction whereas other workers have implicated a failure of the peripheral vasculature as an important factor in the pathogenesis of cardiogenic shock.[15]

The fact that TPR increased significantly in cardiogenic shock does not support the concept that a failure of the total peripheral vasculature occurs after embolization. The marked decreases in cardiac output and superior mesenteric artery flow observed were associated with significant increases in total peripheral resistance and superior mesenteric artery resistance, respectively. Total peripheral resistance increased significantly within 1 hour after embolization and continued to rise throughout the 5 hour postembolization period. The heart rate of dogs in cardiogenic shock, however, did not significantly increase at any time after embolization.

The finding that TPR increased during cardiogenic shock indicates that sympathetic activation was provoked by the hypotension following coronary embolization. However, the central sympathetic response (i.e., increase in heart rate) was not observed. A possible explanation for the failure of the myocardium to respond to central sympathetic activation may be that little undamaged myocardium is available or that the special conduction system or S-A node is damaged. Bing and coworkers[17] have shown that compensation of the myocardium following infarction is due to enhanced action of the uninvolved portion of the myocardium rather than to the improvement of circulation in the involved portion. They further suggested that the unresponsiveness of the uninvolved portion of the myocardium may lead to circulatory failure. On the other hand, the presence of arrhythmias may be indicative of dysfunction in the special conduction system as a result of either damage or altered excitability.

Splanchnic hypoperfusion has been suggested as a common denominator in a variety of shock states, including cardiogenic shock.[18] Lefer[6] has reported that a myocardial depressant factor accumulates in the plasma of animals in a number of states of circulatory shock where splanchnic hypoperfusion is the common denominator. In the present study, splanchnic vascular resistance increased to 2.5 times the control level and was maintained at this level for 2 hours prior to the accumulation of MDF in the plasma. The importance of splanchnic ischemia in the formation of MDF was demonstrated by Wangensteen and associates.[11] These investigators were able to show that celiac blockade and subsequent maintenance of splanchnic flow during endotoxin shock prevented the formation of MDF and resulted in a significant increase in myocardial performance and survival time.

Lillehei and associates[14] have demonstrated that phenoxybenzamine an alpha-adrenergic-blocking agent, prevented the severe vasoconstriction of the splanchnic vasculature and increased survival in cardiogenic shock.

A number of workers[19, 21] have suggested that the release of lysosomal enzymes from the splanchnic region during periods of splanchnic hypoperfusion may be involved in the irreversibility of circulatory shock. However these investigators have not been able to relate the release of lysosomal enzymes to any definite toxic changes.

Lefer and Martin[4] suggested that MDF may be formed by the action of proteases of lysosomal origin. They proposed that the pancreas might be the source of either the activators and/or precursors of MDF since pancreatectomy prevented the plasma appearance of MDF. In hemorrhagic shock and selective pancreatic ischemia resulted in high plasma MDF activities.

More recently Lefer and Glenn[22] have shown that occlusion of the vessels supplying the splanchnic region leads to an increased fragility of pancreatic lysosomes which correlates with increases in plasma lysosomal enzyme activity and with high plasma concentrations of MDF concomitant with hemodynamic changes indicative of circulatory shock.

In the present study the peak reduction in splanchnic blood flow preceded the peak increase in plasma lysosomal enzyme activity. Furthermore the peak rise in plasma lysosomal enzyme activity preceded the increase in plasma MDF activity by 1 hour and correlated well with the occurrence of minimum splanchnic perfusion. This temporal relationship is suggestive of the following chain of events: myocardial damage → hypotension → splanchnic ischemia → lysosomal disruption → MDF production. The production of MDF by virtue of its negative inotropic effect could further aggravate the shock condition. In addition Glucksman and Lefer[23] have shown that MDF exerts a vasoconstrictor action on isolated superior mesenteric artery strips. This constrictor action of MDF on the vascular smooth muscle of the splanchnic bed could result in further vasoconstriction and in prolongation of splanchnic ischemia with the continued production of MDF. Thus a positive feedback loop engendered by MDF may act to maintain a state of shock.

The data obtained in this study suggest the need for a re-evaluation of the existing therapeutic measures employed in the treatment of cardiogenic shock. Sympathomimetic agents would intensify the degree of splanchnic vasoconstriction and could thus contribute to the formation of MDF. Ouabain,[24] a digitalis glycoside has been shown to exert a potent vasoconstrictor action on the splanchnic vasculature. This may be an important consideration in cardiogenic shock where digitalis preparations are frequently employed as cardiotonic agents.[25] Pharmacologic doses of glucocorticoids have also been suggested as being beneficial in cardiogenic shock.[14] Glucocorticoids, if given in pharmacologic doses soon after embolization should be of significant benefit in preventing the formation of MDF but would not directly assist in the restoration of cardiac function. Previous investigators have demonstrated that methylprednisolone not only prevents the plasma accumulation of MDF but also markedly affects the hemodynamic alterations present in both hemorrhagic[26] and bowel ischemic shock.[27] Glenn and Lefer[27] have suggested that methylprednisolone exerts a protective effect by decreasing the sensitivity of splanchnic lysosomes to ischemia and thus reducing the release of lysosomal enzymes into the systemic circulation.

In summary it is suggested that decreases in splanchnic blood flow secondary to a reduction in cardiac output produced by coronary artery embolization leads to the activation of splanchnic lysosomes presumably of pancreatic origin. The proteases which are released are thought to participate in the formation of a cardiotoxic factor MDF which may contribute to the myocardial impairment seen in cardiogenic shock.

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Directional transcutaneous assessment of venous inflow

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Rhythmic fluctuations in venous inflow are reflections of intracardiac events. The origin of such events and the degree to which they facilitate or impede venous return remain open to question. Investigation of superior caval flow in dogs has produced divergent results. Brecher[1] advanced the hypothesis that venous inflow is augmented by ventricular events, whereas Brawley and associates[2] related phasic changes in flow to pressure fluctuations within the atrial cavity. Conflicting data are available from investigation in human subjects to resolve the question of the relative importance of atrial and ventricular activity upon venous return.

A technique for noninvasive transcutaneous measurement of venous flow in the axillary vein, using a bidirectional ultrasonic flow detector, has been utilized to correlate flow profiles with electrocardiographic and venous pressure data. The purpose of this report is to demonstrate the dominant role of the atrium in determining the character of venous inflow in man by comparison of normal individuals with those having selected alterations in cardiac physiology.

Methods

With the use of the bidirectional ultrasonic velocity detector, venous flow velocity was monitored in the proximal axillary vein in 70 patients. Whenever possible, pressure variations within the external jugular vein or right atrium were recorded through a 19 gauge needle or a 24 inch 14 gauge polyethylene catheter. A linear differential transformer pressure transducer, a carrier preamplifier, and a high frequency response recorder were used to reproduce pressure changes. Time correction factors were applied for pulse wave transmission time within the catheter and connecting tubes when pressure and velocity data were compared.

The bidirectional velocity detector utilizes a 10 mHz. ultrasonic beam emitted by one of a pair of piezoelectric crystals. The beam is transmitted transcutaneously and reflected from moving blood particles. The backscatter, altered in frequency by the velocity of the moving blood particles, is then received by the second piezoelectric crystal. The frequency of the ultrasound is increased by collision with blood particles moving toward the probe and decreased by

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collision with particles moving away from the probe. This altered frequency is then electronically compared with the original frequency and the difference presented to one of two identical circuits. Frequency shifts above 10 mHz. are switched to the first audio output circuit and electronic integrator which produces a signal representative of flow toward the probe. Frequency shifts below 10 mHz are switched to a second identical circuit producing an output representative of flow away from the probe Forward and reverse flow therefore can be recorded separately

Patients were studied in a supine position after they had been familiarized with the surroundings and experimental procedure. The arm was placed in a relaxed position by the patient s side although changes in arm positioning proved to have no effect on the venous records. The same parameters were recorded on all patients and included (1) electrocardiogram (ECG) (2) flow toward the heart (forward flow) (3) flow away from the heart (reverse flow) (4) jugular venous pressure and/or central venous pressure and (5) phonocardiogram. Similar parameters were studied n patients after exercise and at various angles on a tilt table Tracings in a semirecumbent position were also attempted

Results

Of the 70 patients studied 34 were shown to have normal cardiovascular systems by history and physical examinations. Thirteen patients had moderate to severe congestive heart failure whereas three had very mild manifestations of this condition. Twelve patients were in atrial fibrillation Three patients had complete heart block and were being paced with a transvenous pacemaker at the time of the study Five patients had severe right heart hypertension and chronic right heart failure.

Normal cardiac dynamics The normal group of patients had inflow velocity profiles similar to those represented in Fig. 1 Axillary vein inflow in a single cardiac cycle was found to have two peaks, one in midsystole (Fig 1 *B*) and the other during middiastole (Fig. 1 *D*) At the end of systole flow toward the heart decreased somewhat, giving a notched appearance to

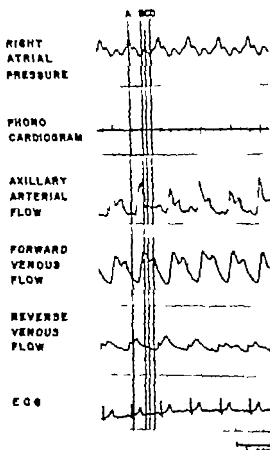


Fig 1 Venous return monitored transcutaneously in the subclavian vein of normal individual. Recordings are simultaneous with the same time base. *A* Flow reversal due to atrial contraction *B* peak of inflow phase occurring during ventricular systole *C*, end systole, completion of atrial filling *D* opening of the tricuspid valve, diastolic filling. Forward venous flow refers to flow into the heart reverse venous flow is flow away from the heart.

the forward flow profile. This relative minimum lagged approximately 0 06 second behind the v wave of the venous pressure tracing (Fig 1 *C*) A short period of reverse flow was often but not consistently recorded synchronous with the "v" wave (Fig 1 *C*) The diastolic forward flow peak then occurred (Fig 1 *D*) followed by a rapid deceleration of the flow profile which decreased approximately one half to two thirds of its peak value before atrial systole occurred A sharp flow reversal was consistently seen coincident with the a pressure wave of atrial systole (Fig 1 *A*) Forward flow continued to decrease during the time of this reversal and reached a

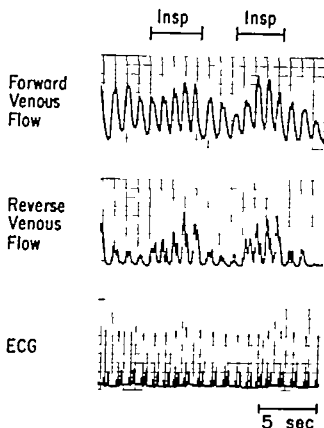


Fig. 2. Subclavian vein flow during normal respiration. Forward and reverse flow both increase during inspiration.

minimum level at the peak of the c wave of the pressure tracing. With atrial relaxation and the onset of the next ventricular systole, the inflow again increased rapidly.

A delay of 0.10 to 0.30 second was observed from the peak of the P wave of the ECG to the peak of the reverse flow curve. The average delay time was 0.16 second. This time proved to be shorter in patients with cardiovascular disease; however, no consistent time delay was characteristic of any type of heart lesion. In every case, the delay in the onset of the atrial reversal was accompanied by an equal delay in the a wave of the pressure recording.

Tracings made during normal breathing revealed increased forward and reverse velocity during inspiration while both diminished markedly during expiration (Fig. 2). Recordings made after mild and severe exercise failed to reveal significant changes in the flow profile or its timing within the cardiac cycle. In addition, changes of position from head up 15° to head down 30° failed to produce different velocity patterns. Tilting beyond 15 to 20° in the head up position resulted in an abrupt increase in velocity flow and obliteration of discernible retrograde pulses. The reason this increase in velocity occurs is not known; however, the event may be related to partial collapse of the axillary vein at that point.

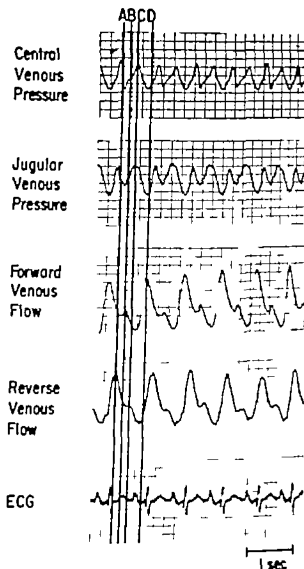


Fig. 3. Simultaneous tracings from a patient with congestive heart failure. *A*, Large atrial reversal is synchronous with atrial contraction. *B*, systolic inflow period. *C*, reverse flow at the end of systole occurring simultaneously with the v pressure wave. *D*, diastolic inflow phase.

Right ventricular hypertension and chronic uncompensated congestive heart failure. Four patients with right ventricular hypertension and chronic right heart failure were studied. All four had clinical and roentgenological right heart hypertrophy and edema marked by elevated venous pressure. All patients had identical changes in their axillary

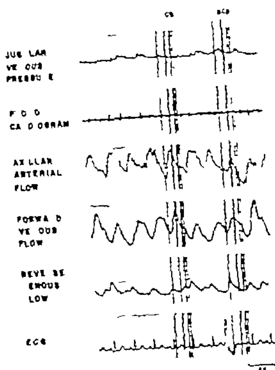


Fig. 4 Simultaneous ECG, forward and reverse flow recordings from a patient with premature ventricular contractions. *A* Atrial reversal occurring after the P wave of sinus beat and during premature beat *B* systolic inflow *C*, decrease in forward flow and flow reversal t the end of systole *D* diastole inflow period.

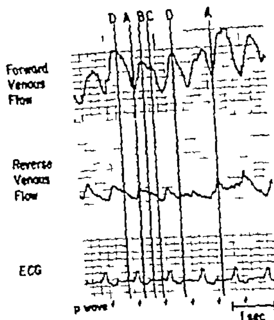


Fig. 5 Simultaneous recording of venous inflow in patient with atrioventricular dissociation paced with transvenous pacemaker *A* Flow reversal following the P w ve *B* venous inflow during the period of trial relaxation *D* Inflow during ventricular relaxation *D'* single inflow phase in a cardiac cycle with simultaneous ventricular and atrial relaxation.

velocity profile The diastolic inflow phase (Fig 3 *D*) overshadowed the small systolic inflow peak (Fig 3 *B*) and the shallow notch coincident with the "v" wave became much more pronounced (Fig 3 *C*)

Disturbances of atrioventricula coordination In ten patients with multiple premature ventricular contractions, velocity recordings were similar to those illustrated in Fig. 4. Both atrial reverse flow (Fig 4 *A*) and early systolic inflow (Fig 4 *B*) occur at a time which is unrelated to the first heart sound produced by the premature beat. Instead the intervals are that of an atrial beat occurring at its expected time in the cardiac cycle. The reverse flow peak does not occur prematurely as does the QRS complex and other recorded events of the cardiac cycle but maintains the same periodicity as preceding reversals following sinus beats (Fig 4 *A*) The effect of such a sequence of events is to increase the temporal separation between the premature QRS complex and this regularly t med flow reversal.

Fig 5 is a record from a patient with a complete heart block who was being paced by a transvenous pacemaker This patient was representative of the three who were studied. All had experienced sudden onset of syncope and were found to have complete heart block with ventricular rates in the 40 to 50 range. In all three permanent transvenous pacemakers had been implanted and a synchronous atrial and paced ventricular beats were observed on the ECG The P waves were asynchronous with the QRS complexes. Each P wave was followed by an instantaneous atrial reversal which peaked approximately 0.24 second after the peak of the P wave (Fig. 5 *A*) and a forward flow peak occurring approximately 0 40 second after the peak of the P wave (Fig 5 *B*) The same pattern was recorded regardless of the position of the P wave in the cardiac cycle. The diastolic inflow peak was unchanged in its timing however the interval between the systolic

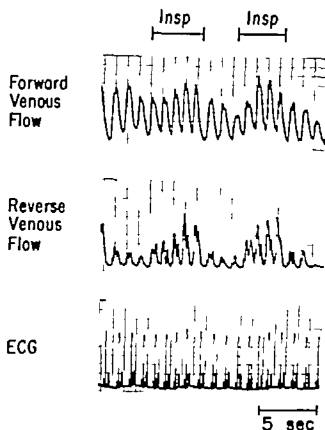


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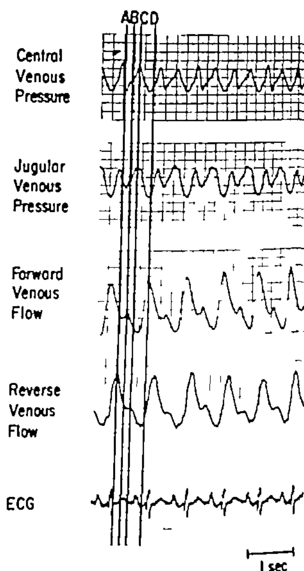


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dissociation had been induced. In both studies, ventricular contraction without a preceding atrial contraction resulted in either a minimal increase in flow or an actual decrease. Isolated atrial beats, on the other hand, were followed by a large venous inflow at the time of atrial relaxation. Such studies emphasize the dominant role of the atrium in regulating venous return. On the other hand, Wexler and associates, using a catheter tip electromagnetic flowmeter, described the usual systolic augmentation of flow in a human subject with atrial fibrillation.

The results of the present study using the ultrasonic flow detector support the hypothesis of Brawley and Pinkerson that atrial relaxation rather than systolic suction causes the systolic inflow in normal individuals. Recordings from the axillary vein demonstrate that no systolic inflow is present in patients with either premature ventricular contractions or atrial fibrillation. In addition, tracings from persons with atrioventricular dissociation reveal the presence of a forward flow peak approximately 0.45 second after the apex of the electrocardiographic P wave regardless of the P wave's location in the cardiac cycle. This inflow period follows immediately after the flow reversal associated with atrial contraction and should be synchronous with atrial diastole. No systolic inflow is present in these patients.

Benchimol and co-workers, using an ultrasonic catheter flowmeter, described a velocity wave which occurred approximately 0.09 to 0.10 second after the P wave of the ECG. They surmised that this wave was a result of atrial systole and represented retrograde flow. Such reversed flow was observed constantly in the group of normal individuals studied with the bidirectional velocity detector; however, the time interval averaged 0.16 second after the peak of the P wave (range 0.10 to 0.35 second). In addition, patients with complete heart block had flow reversals following each P wave, again in spite of its position in the cardiac cycle. This evidence strongly supports the hypothesis that atrial contraction results in a significant reverse flow.

Comparison of Benchimol's "A" wave to those atrial reverse flow peaks found in this study reveals a 0.06 second discrepancy in its average occurrence after the P wave of the ECG. A large part of the discrepancy might be explained by the longer distance the propagated waves travelled before reaching the transducer. Work done in this laboratory indicates that pulse waves propagated by intracardiac events move at various speeds, dependent on many factors, and are variable by a factor of four in veins the size of the vena cava.

Examination of forward and reverse flow profiles obtained with the bidirectional ultrasonic velocity detector reveals that most flow reversals overlap with a significant amount of forward flow. It is doubtful that such simultaneous forward and reverse flow represents an error in signal discrimination. Simultaneous bidirectional flow does occur experimentally in elastic tubes and arteries.[22,23] Pulsatile blood flow produces a velocity profile which is initially forward and expanding. During the diastolic or resting phase the profile collapses as the velocity decelerates. The fluid adjacent to the wall of the tube actually reverses its direction instantaneously while the fluid at the center line maintains forward velocity. Such an experimental model could logically be applied to the great veins. As in the arterial system, the pulse generator is the heart; however, the pressure differentials which produce the velocity changes are propagated in a retrograde direction.

The proximal axillary vein has been selected as the preferential site for monitoring venous inflow because of its excellent dynamics, accessibility, and close proximity to the right atrium. It is easily found just inferior to the clavicle as it crosses the second rib and from this point can be followed peripherally until an optimum signal is obtained. In the absence of a good signal infraclavicularly, the vein can be found high in the axilla. Simultaneous arterial and venous ultrasonic recordings at these sites reveal that no arterial events are superimposed on any of the major venous flow waves.

Summary

Venous inflow was monitored in the axillary vein of 70 individuals with the use of a

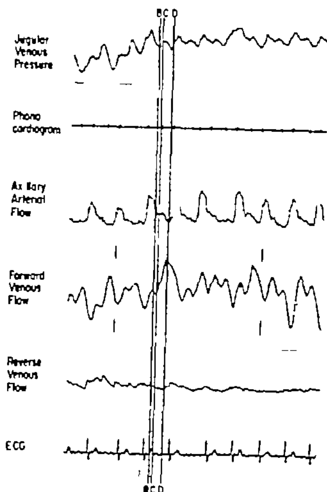


Fig. 6. Flow tracings of a patient with atrial fibrillation. *B* denotes the diminutive systolic inflow phase followed by *C* diminishing velocity before diastole. *D* represents diastolic inflow.

and diastolic inflow peaks varied continuously apparently dependent upon the position of the f wave in the cycle.

Patients studied with atrial fibrillation had some degree of mild compensated congestive heart failure but no other major cardiac lesions. In these patients the major portion of venous return was limited to diastole (Fig. 6 *D*). Flow reversals were occasionally present and closely followed changes in the venous pressure pulse. The atrial reversal was usually absent but was occasionally seen in coarse flutter fibrillation. In some patients a large pansystolic reverse flow peak was seen and probably represented tricuspid insufficiency coexistent with atrial fibrillation.

Cardiac abnormalities with no detectable velocity changes. Thirteen patients with congestive heart failure had no detectable velocity changes in the axillary vein which differed from normal individuals. Qualitatively no changes were documented in the relative magnitude of forward and reverse flow with increasingly severe compensated cardiac failure. Exercise, tilting from head up 15° to head down 30° and semierect posture had no effect on timing of venous inflow or the contour of the velocity profile.

Discussion

Several recent studies have demonstrated the usefulness of the ultrasonic flow detector in the investigation of cardiac effects on venous inflow. Bellet and Kostis[4] utilized the ultrasonic flow detector transcutaneously in patients with various arrhythmias. By noting the presence or absence of an atrial wave they were able to obviate the necessity of esophageal or intracardiac leads in cases impossible to diagnose by usual electrocardiographic means. Benchimol and colleagues[5] used an ultrasonic catheter flowmeter telemetry system to describe venous flow in normal individuals and those with a variety of heart lesions. This group concluded that the technique was of value in assessing flow velocity under a variety of physiological conditions. The addition of bidirectional velocity detection has simplified interpretation of venous inflow tracings. Furthermore, the ability to measure such events transcutaneously greatly facilitated the acquisition of data under entirely physiological conditions.

The relative importance of the atrium on phasic changes in venous return has received considerable debate. Eckstein and associates[6] noted a rise in venous inflow during ventricular systole and inferred that this rise took place as a result of some unspecified action of the ventricle upon atrial pressure. Brecher[1,7] and Brecher and Hubay[8] popularized the hypothesis that the heart acts like a reciprocal pump, that is, the action of the descending atrioventricular ring during systolic ejection actually draws blood into the atrium. This concept was supported by the temporal coincidence of the venous inflow with systolic ejection in dogs. Brawley and associates[3] as well as Pinkerson and associates[9] have questioned the validity of this cause-and-effect relationship. Both groups studied dogs in which atrial fibrillation and atrioventricular

Case reports

Right coronary artery to left ventricle fistula

A case report and discussion

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Congenital coronary arterial communications with either ventricle or either atrium are rare. There have been only two previous reports of right coronary artery to left ventricle fistulas.[1,2] This paper presents a case of such a lesion that was successfully corrected at surgery after being diagnosed by cardiac catheterization and angiocardiography. The development of the lesion is discussed and it is suggested that this entity represents two separate embryologic anomalies.

Case history

A 4-year-old boy was referred to the Flower Fifth Avenue Hospital for evaluation of a murmur heard first at one year of age and thought to be due to aortic insufficiency. The mother's pregnancy was complicated by hypertension during the last trimester; the delivery was normal. The birth weight was 7 pounds, and cyanosis was observed at birth but disappeared within one hour. The child was subject to frequently occurring upper respiratory infections. There was no history of chest trauma, edema, syncope, or chest pain. The child was observed at another hospital from age one year to the time of referral, but definitive cardiac diagnostic studies were never performed.

Physical examination revealed a well-developed, well-nourished, Negro boy who was in the fiftieth percentile for weight but the third percentile for height. The pulse rate was 86 per minute and regular and the blood pressure was 110/60 mm. Hg. There were symmetrically full peripheral pulses. No cyanosis or clubbing was observed, and the point of maximum impulse (PMI) was in the 6th, left intercostal space, 1 cm. outside the midclavicular line. There was a distinct left ventricular lift. A Grade 3/6 harsh, ejection, systolic murmur was heard at the lower left sternal border followed by a Grade 3/6, decrescendo, diastolic murmur heard best at the third, left intercostal space and transmitted down the left sternal border. No thrills were palpable. P₂ was normally split and was greater than A₂. Phonocardiography confirmed these findings. The remainder of the physical examination was unremarkable except for meatal stenosis of the urethra. An electrocardiogram (Fig. 1) demonstrated evidence of left ventricular hypertrophy. A chest roentgenogram (Fig. 2) revealed slight cardiomegaly with normal pulmonary vascular markings. Complete blood count (CBC) and urinalysis were normal.

Right and left cardiac catheterization were performed. Through a *right brachial* venotomy a No. 6 Rodriquez catheter was passed into the right side of the heart. Pressure and oxygen saturation values were normal, and no left-to-right shunt could be demonstrated. A right brachial arteriotomy was performed, and a No. 6 Rodriquez catheter was passed into the left ventricle with no gradient observed across the aortic valve. Angiocardiography was performed from both the left ventricle and the root of the aorta demonstrating a large, tortuous, right coronary artery arising from a dilated anterior coronary sinus and progressing anteriorly and then

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defect with aortic insufficiency due to a prolapsed right anterior or noncoronary aortic cusp. This clinical diagnosis was reached after consideration of three major diagnostic criteria and before cardiac catheterization and angiocardiography were performed. The first of these was the presence of the combined systolic and diastolic murmurs. These murmurs are found in coronary artery fistulas, ruptured sinus of Valsalva, aortic pulmonary window, patent ductus arteriosus, and arteriovenous fistulas of the mediastinum and chest wall. Associated systolic-diastolic murmurs are also heard in pulmonary arteriovenous fistulas, but this defect is usually accompanied by cyanosis and polycythemia. Isolated aortic insufficiency due to rheumatic heart disease or Marfan's syndrome were considered unlikely because of the age of the patient at the time the murmur was first heard, and the fact that he had no stigmata of Marfan's syndrome.

The second major sign was electrocardiographic evidence of left ventricular hypertrophy. This electrocardiogram made a coronary artery to right side of the heart fistula unlikely since, in this entity combined right and left ventricular hypertrophy can be anticipated as well as the appearance of right ventricular conduction disturbances.

The last of the major diagnostic criteria was the lack of increased pulmonary vascular markings in the presence of cardiac enlargement. All of the previously considered lesions exhibit an increase in markings except a ruptured sinus of Valsalva communicating with the left ventricle, aortic insufficiency with ventricular septal defect and prolapsed coronary cusp occluding the defect, and coronary artery fistula to the left side of the heart.

Cardiac catheterization failed to demonstrate a left-to-right shunt or a gradient across the aortic valve which effectively ruled out the diagnosis of aortic insufficiency with ventricular septal defect as well as coronary artery to right side of the heart fistula. Thus, two remaining diagnoses were possible: a ruptured sinus of Valsalva or a coronary artery to left ventricular fistula. Statistically if the latter defect were present, it most likely consisted of a communication between the left coronary artery and the left ventricle.[3] The definitive diagnosis of the lesion was not made until angiocardiography was performed.



Fig. 2. Chest roentgenogram on admission. Note cardiomegaly with normal pulmonary vascular markings.

In coronary artery fistulas, the auscultatory findings are usually caused by flow through the fistula. Systolic or diastolic accentuation of the murmur is directly related to the pressure in the chamber with which the fistula communicates.[4] The murmur is usually continuous, but separate systolic and diastolic murmurs have also been described.[5] The murmur is usually heard best at the right and left lower parasternal areas, the xiphoid, or the mid precordial area. Normally coronary arterial blood flow into the left ventricle occurs mostly during diastole. The presence of a large low resistance fistula in the wall of the left ventricle greatly increased the flow during both systole and diastole to account for the systolic as well as the louder and longer diastolic murmur.

Congenital coronary artery fistulas have been reported with increasing frequency in the past ten years. Of 168 cases surveyed

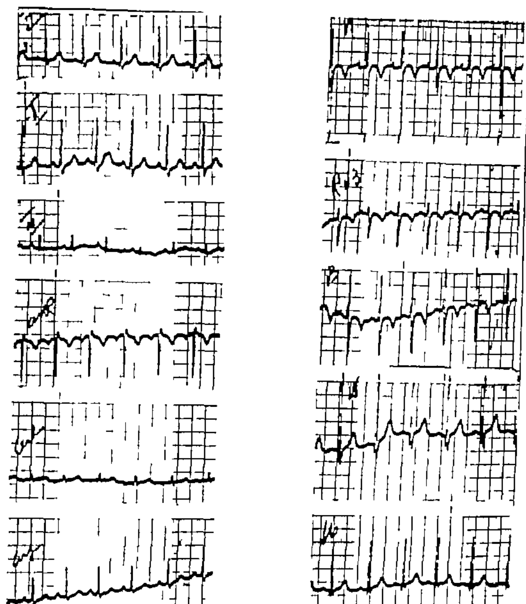


Fig 1 Electrocardiogr m on admission showing evidence of left ventricular hypertrophy with deep S in a V_R and V_{4R}

inferiorly The contr t medium was observed to empty into the left ventricle (Figs. 3 and 4) The entire myocardium of the left ventricle opacified uggesting perfusion of the posterior myocardi m by the right coronary artery The course and di tribution of the left coronary artery was thought to be normal at the time of catheterization.

Surgery was performed when the patient was *four years and ten months of ge The heart was* moderately enlarged nd a large right coronary artery was noted which arose normally nd gave off many branches to the right ventricular myocard um as it passed in to the atrioventricular groove to the diaphragmatic aspect of the heart. At the inter ventricular groove posteriorly *the artery continued* to the atrioventricular groove between the left atrium and the left ventricle. The artery then d pped to the substance of the left ventricular wall just below the atrioventricular groove. There wa a marked dilatation of the artery at this poi t. I this area of the left ventricular wall a thrill was palpable which disappeared when finger pressure was applied to the rtery After careful observation of the electrocardiogram for several minutes t insure adequacy of myocardial perfusion, the vessel was doubly ligated. It was observed at this time that the left circumflex artery had no posterior descending branch but that a small communicating artery joined the right posterior descending branch

After urgery both murmurs disappeared A chest roentgenogram (Fig 5) three month postoperat vely showed normal cardiac size with normal pulmonary vascular markings, although the electrocardiogram continued to demonstrate left ventricular hy pertrophy An electrocardiogram three years after surgery *showed no evidence of left ventricular* hypertrophy (Fig 6)

Discussion

When first seen at four years of age the *patient was felt to have a ventricular septal*

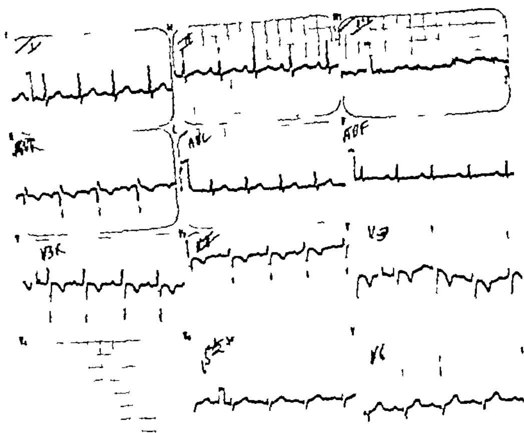


Fig. 5 Electrocardiogram three years after surgery showing normal electrocardiographic pattern for age.

spaces allowed it to communicate directly into the left ventricular cavity. The absence of a left, descending circumflex artery probably resulted from the complete closure of all main sinusoids of the posterior myocardium in that area. Only a small communicating branch of a size insufficient for adequate perfusion brings left coronary artery blood to the posterior myocardium. Thus, the resulting anomaly arises from two separate embryological defects.

Summary

A case of a 4-year-old boy with a history of fatigue and a heart murmur is presented. Cardiac catheterization revealed a right coronary artery to left ventricular fistula. The fistula was ligated at surgery after which the heart size decreased, the murmur disappeared, and the electrocardiogram became normal. The differential diagnosis is discussed, and the embryological aspects of the development of the lesion are presented.

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Fig. 3. A and B. Aortic root angiograms showing coronary flow through dilated anterior coronary sinus and right coronary artery (1) emptying into the left ventricle (B).

61 per cent involved the right coronary artery and 39 per cent the left coronary artery. The great majority of right coronary fistulas (96 per cent) involved the right side of the heart; only 4 per cent involved the left side. Similarly, 81 per cent of left coronary artery fistulas communicated with right heart chambers and 19 per cent with left heart chambers.[3] The only previous report of right coronary artery to left ventricular fistula in the English literature describes a fistula into the left ventricle just below the aortic valve.[8] In the present case the right coronary artery emptied into the left ventricle at the apex of the heart after following a normal course; therefore, it represents a different developmental anomaly. A case that apparently has an anomaly similar to the present case has been reported in the Japanese literature.[1]

Embryologically, the early coronary circulation consists of wide endothelial-lined spaces between the muscle columns of the heart with outgrowth toward the epicardial surface. Intratrabecular sinusoids freely communicate with these new epicardial vessels. As the myocardium grows, the intratrabecular spaces become obliterated until only microscopic capillary channels remain. If there is an arrest of this process, the intratrabecular spaces remain as fistulous communications between the coronary artery and the heart cavity.[4]



Fig. 4. Chest roentgenogram three months postoperatively demonstrating normal cardiac silhouette.

Furthermore, if the intratrabecular spaces coalesce irregularly, the coronary arteries themselves may become anomalous. In this case it was noted that both the left and right circumflex arteries emptied into a single posterior descending coronary vessel. A similar anomaly has been described by Edwards.[4]

In the present case the course of the right coronary artery was normal until it reached the posterior myocardium, where a defect in the closure of the intratrabecular

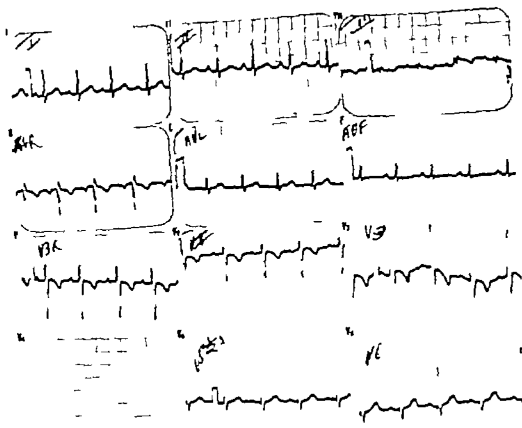


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Summary

A case of a 4-year-old boy with a history of fatigue and a heart murmur is presented. Cardiac catheterization revealed a right coronary artery to left ventricular fistula. The fistula was ligated at surgery after which the heart size decreased, the murmur disappeared and the electrocardiogram became normal. The differential diagnosis is discussed, and the embryological aspects of the development of the lesion are presented.

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Subclavian steal syndrome in right aortic arch with isolation of the left subclavian artery

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Contorni[1] and Reivich and associates[2] first described patients with proximal subclavian artery obstruction in which circulation to the arm was maintained by retrograde flow down the vertebral artery with drainage of blood away from the basilar territory of the brain. This reversal of blood flow in the vertebral artery may cause basilar artery insufficiency, and the symptoms and signs resulting from ischemia of the brain stem have been termed the subclavian steal syndrome.[3]

Many causes of the subclavian steal syndrome have been described and include atherosclerosis,[4,5] Takayasu's arteritis,[6] tumor thrombus,[7] embolic occlusion,[8] surgical ligation of the subclavian artery in the Blalock-Taussig anastomosis,[9] and congenital atresia of the subclavian artery.[10-12]

Right aortic arch with the left subclavian artery no longer connected to the aorta (isolation of the left subclavian artery) is a rare congenital anomaly[13] and an unusual cause of subclavian steal.[14] For this reason it was considered of interest to describe such a case with angiographic demonstration of reversal of blood flow in the left vertebral artery. In addition, the importance of extracerebral collateral channels as a source of blood supply to the left upper extremity in this patient will be emphasized.

Case report

L. D. W., 36177, a 23-year-old soldier, was first seen at Grady Memorial Hospital at age 4 years with acute glomerulonephritis. Blood pressure in the right arm was 160/120 mm. Hg and no information is available regarding pulse or blood pressure in the left arm. The patient responded well to treatment and on routine follow-up visits at age 7 chest x-rays disclosed a right aortic arch. The blood pressure in the right arm was 98/60 mm. Hg and blood pressure was unobtainable in the left arm. He was asymptomatic with normal growth and development.

The patient was subsequently followed in the cardiac clinic because of the aortic arch anomaly. At age 12 he first noticed that his left arm felt like it was going to sleep, and that it tired easily. As a result, he used his right hand for almost everything. However, he was able to actively participate in sports without difficulty.

At age 18 the patient complained of numbness in the left upper extremity of two months' duration which occurred when his arm was raised above the left shoulder. Except for easy fatigue in the left upper extremity, there was no difference between his two arms in his ability to lift weights. There was no history of injury to his left arm, or symptoms

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Fig. 1 Aortogram shows opacification of the left common carotid, right common carotid, and right subclavian arteries only from the arch. The aorta descends on the right. (From Shuford, W. H. Sybers, R. G., and Schlant, R. C. Amer J Roentgenol., May 1970 published by Charles C Thomas, Publisher.)

to suggest congenital heart disease or cerebral or vertebrobasilar insufficiency

The patient was admitted for aortography. H was well developed and appeared in good health. Auscultatory blood pressures were right arm, 118/50 mm. Hg arm raised to shoulder level, 110/50 mm. Hg left arm, 80/56 mm. Hg arm raised t shoulder level, 70/60 mm. Hg right leg, 140/80 mm. Hg and left leg, 138/70 mm. Hg. The pulses in the left pper extremity ere weaker than in the right and disappeared when the left arm was ised above the shoulder Both carotid and femoral pulses ere palpable equally A continuous murmur was audible over the posterior triangle of the neck on the left side. Examination of the heart and the neurological examination revealed normal findings. The electrocardiogram was within normal limits.

Chest roentgenograms disclosed right aortic arch, normal-sized heart, and normal pulmonary vasculature. Barium swallow revealed no abnormal indentation on the posterior esophageal wall.

The aortogram showed the aorta to descend on the right side. The left common carotid artery arose as the first branch from the arch and was followed by the right common carotid and right subclavian arteries. The lef subclavian artery did not opacify from the arch (Fig. 1)

Selective injection of the left common carotid artery was then performed (Fig 2, *A*) Two seconds following injection the distal left subclavian artery as opacified by collateral channels from the left external carotid artery through the vertebral artery and branches of the thyrocervical and costocervical trunks (Fig. 2, *B* and *C*)

Cerebral arteriography with injection of the left common carotid artery revealed no evidence of arterial flow up the left internal carotid artery through the circle of Willis to supply the left arm (Fig 3)

Upon catheterizing the left brachial artery the catheter met resistance in the first or thoracic portion of the left subclavian artery Hand injection of radiopaque material revealed this portion of the left subclavian artery t end blindly There wa no luminal connection of the left subclavian rtery either with the aorta or with the pulmonary arterial system. The vertebral br nch nd costocervical nd thyrocervical trunk of the left subclavian artery opacified for short distance (Fig. 4 *A* nd *B*).

Catheter pressures in the scending aorta were 73/40 mm. Hg with mean of 60 mm. Hg, and in the left brachial artery 75/52 mm. Hg with a mean of 63 mm. Hg

Discussion

In their monograph on malformations of the aortic arch Stewart, Kincaid and Edwards[illegible] classify right aortic arch into three major types (1) with *mirror-image* branching of the major arteries (2) with an aberrant left subclavian artery and (3) with the left subclavian artery isolated from the arch

Right aortic arch with isolation of the left subclavian artery is the least common of the three types.[illegible] Knowledge concerning this malformation has resulted chiefly from the study of anatomic specimens.[illegible] In this entity the left common carotid artery arises as the first branch of the aorta to be followed by the right common carotid and the right subclavian arteries in that order The left subclavian artery no longer has a connection with the aorta but arises from the left pulmonary artery by way of a left ductus arteriosus (Fig 5)[illegible]

Chest roentgenograms in these patients show the aortic arch to be anterior and to the right of the trachea and esophagus. The barium swallow shows no compression on the posterior esophagus. This anomaly is frequently associated with cyanotic congenital heart disease, especially the tetralogy of Fallot.[illegible] In our patient there was no evidence for a congenital malformation within the heart.

When the first or thoracic portion of the left subclavian artery is absent or obstructed, blood may reach the left arm by one of several pathways. Retrograde flow down the left vertebral artery represents the final common pathway of many



Fig 2A Selective injection of the left common carotid artery (From Shuford W H Sybers, R G, and Schlant R C Amer J Roentgenol May 1970 published by Charles C Thomas, Publisher)



Fig 2B Subtraction arteriogram two seconds after injection. The distal left subclavian artery opacifies by collateral channels from the left external carotid artery through the vertebral artery and branches of the thyrocervical and costocervical trunks. (From Shuford W H Sybers, R G and Schlant R C: Amer J Roentgenol. May 1970 published by Charles C Thomas, Publisher)

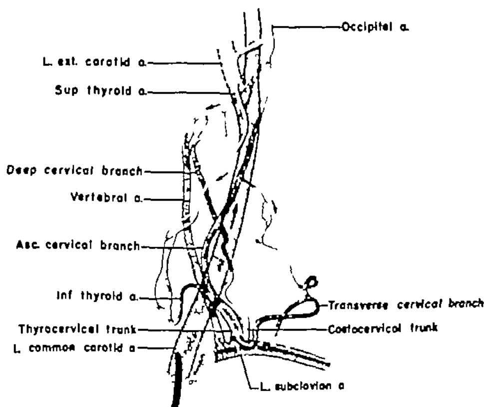


Fig 2C. Composite drawing of Fig 2 A and B



Fig. 3 Selective injection of the left common carotid artery. There is no evidence of flow through the circle of Willis contributing to the blood supply of the left subclavian artery



Fig. 4A Retrograde injection of the left subclavian artery with catheter tip in its first portion (From Shaford, W. H. Sybers, R. G., nd Schlant, R. C.: Amer. J. Roentgenol., M y 1970, published by Charles C Thomas, Publisher.)

collateral channels (Fig. 6)[4,8,10-12] The first of these is the right vertebral artery which communicates directly with the left vertebral artery at the vertebrobasilar junction. The second collateral route involves the circle of Willis. Blood from either the right or left internal carotid arteries may reach the basilar and left vertebral arteries through the respective right or left posterior communicating and posterior cerebral vessels. In addition to these pathways involving the cerebral and basilar artery circulations, a third route the cervical arterial collateral network, utilizes the occipital branch of the external carotid artery the muscular branches of the vertebral artery and the thyrocervical and costocervical trunks of the subclavian artery. Anastomoses between the superior and inferior thyroid arteries and pathways between the thyroid arteries of the opposite side may occur. Finally anastomoses by way of the internal mammary and intercostal arteries and anastomoses between the intercostal arteries and branches of the axillary artery may be present, but are of lesser importance

In most patients with the subclavian steal syndrome the right vertebral artery directly supplies the left vertebral artery at the vertebrobasilar junction.[8] In our patient contrast studies of the right vertebral and right carotid arteries were not performed. For this reason the amount of blood flow if any through the vertebrobasilar vertebral route and/or crossover filling from the right carotid artery is not known. Selective injection of the left common carotid artery revealed no flow from the left internal carotid artery through the circle of Willis to the basilar artery and hence to the left arm via the left vertebral artery

Arteriographic studies clearly indicate that a principal source of blood to the left upper extremity was from the left external carotid artery. Selective injection of the left common carotid artery showed blood reaching the distal left subclavian artery via anastomoses between the occipital branches of the external carotid artery and muscular branches of the vertebral artery and anastomoses between the occipital branches of the external



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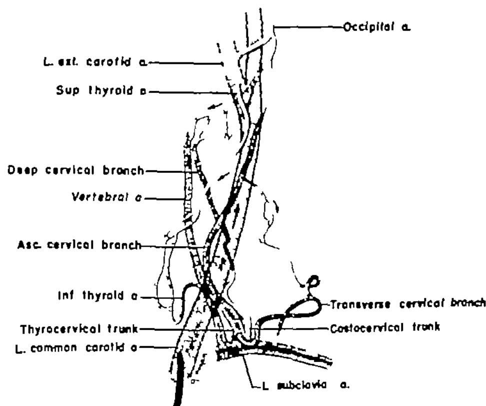


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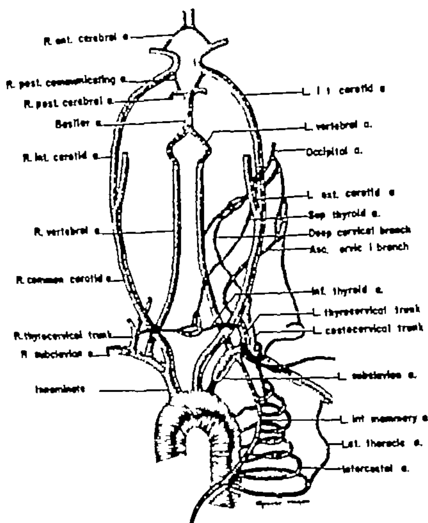


Fig. 4. Diagram of collateral circulation in the presence of occlusion or absence of first portion of the left subclavian artery

blurred vision headaches) arm symptoms (pain, cramps, numbness) a weak or absent radial pulse, a supraclavicular bruit, and a blood pressure difference between the two arms. The only complaints experienced by this patient were secondary to inadequate blood flow into the left arm. These symptoms were of minor nature and did not interfere with his performing duties as a combat soldier. This is not surprising as numerous Blalock Taussig operations have well established that the subclavian artery can be ligated almost without complication.[16]

Also symptoms of brain-stem circulatory ischemia were absent. Undoubtedly the absence of symptoms of basilar artery insufficiency was due to the rich extra cerebral collateral network which developed early in life. It is of interest that in most of the reported cases of subclavian steal syndrome of congenital cause cerebral symptoms have been absent.[6,11,1]

With the exception of the recent report by Maranhao and associates,[14] this case represents the first angiographic demonstration of subclavian steal in this type of congenital malformation of the aortic arch.

Summary

A patient with a right aortic arch and isolation of the left subclavian artery and the subclavian steal syndrome is pre

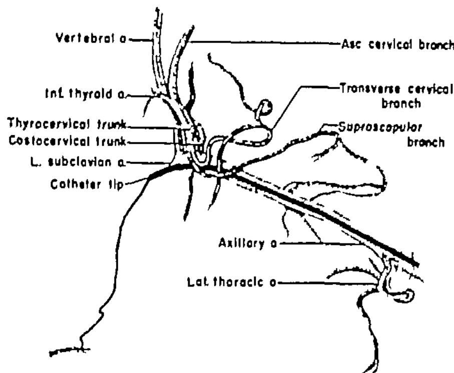


Fig. 4B. No connection of the left subclavian artery with the aorta or the left pulmonary artery is demonstrated.

carotid artery and the thyrocervical and costocervical trunks of the left subclavian artery. In addition, the left superior thyroid artery anastomosed with the inferior thyroid artery to supply the thyrocervical trunk. Bosniak[19] has emphasized the importance of these cervical arterial collateral pathways in patients with brachiocephalic occlusive disease. Virtually all of the possible collateral routes in the neck were functioning in this patient.

With a difference in blood pressure between the aorta and the left arm there exists in this patient a situation similar in reverse to that found in coarctation of the aorta. Theoretically, the congenital collateral pathway that might be expected to be well developed was not present—or at least not demonstrated by contrast studies. Aortography showed no blood reaching the left subclavian artery through the aortic intercostal internal mammary route.

This extracerebral pathway generally is not a source for blood reaching the left arm in the subclavian steal syndrome due to atherosclerosis. However, in subclavian steal resulting from the Blalock-Taussig pulmonary subclavian artery anastomosis the posterior intercostals may be important pathways for collateral flow through

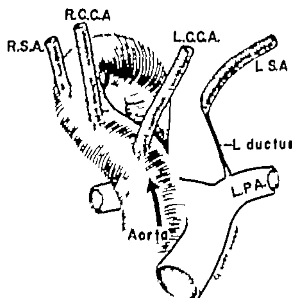


Fig. 5. Right aortic arch and isolation of the left subclavian artery. The left subclavian artery is connected to the left pulmonary artery by the left ductus arteriosus.

their communications with the thoracic and subscapular branches of the axillary artery.[21,24] On occasion rib notching on the side of the anastomosis may be seen in these patients.[24]

Patel and Toole[4] have listed the important features of the subclavian steal syndrome. Most prominent among these are cerebral symptoms (vertigo, dizziness,

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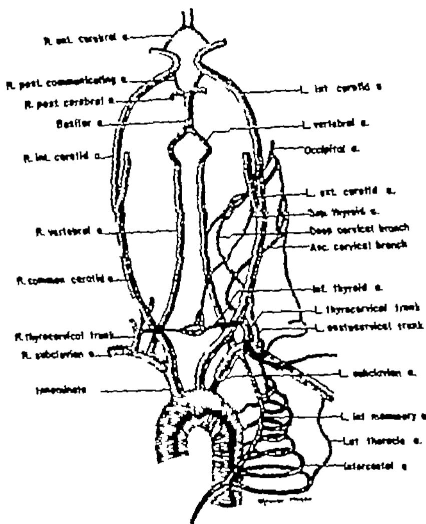


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Summary

A patient with a right aortic arch and isolation of the left subclavian artery and the subclavian steal syndrome is pre-

sented The clinical features resulted from a relative ischemia of the left arm and there were no findings to suggest cerebrovascular insufficiency or congenital heart disease The esophagrams revealed no defect on the posterior aspect of the esophagus Collateral channels from the left external carotid artery opacified the distal left subclavian artery

The causes of subclavian steal syndrome are reviewed together with the pathways for collateral circulation to the left arm when the proximal portion of the left subclavian artery is obstructed

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Review

Myocardial blood flow and oxygen uptake in clinical and experimental cardiomegaly

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The frequent occurrence of cardiomegaly in a great number of cardiovascular diseases and abnormalities as well as its occurrence in healthy athletic individuals and animals has led to extensive studies of the phenomenon both clinically and experimentally Since the hypertrophied myocardium in pathologic states is prone to fail the question of the adequacy of the coronary circulation in the pathogenesis of myocardial failure assumes great clinical significance. Considerable divergence of opinion exists on this question, particularly among those who study the postmortem morphologic aspects of the coronary vascular bed in relation to the mass of hypertrophied muscle fibers. The causes for such differences of opinion are many and varied.

For one thing the stages or degrees of cardiac hypertrophy studied by different investigators are often not comparable. There are at least three distinct stages in the evolution of pathologic hypertrophy of the heart (1) the initial stage of hypermetabolism and growth of muscle fibers, (2) the stage of stable hypertrophy without clinical signs of failure (compensated) and (3) the stage of hypertrophy with signs of failure (decompensated) Meerson refers to these as (1) the stage of damage, (2) the stage of relatively stable hyperfunction, and (3) the stage of cardiosclerosis and gradual exhaustion. The transition from one stage to the other is gradual. Human autopsy material is usually in stage 3 and it is reasonable to expect differences in the morphology of the coronary vessels between stages 2 and 3 The effect of the duration of each stage on coronary vascular structure should also be considered Very often in the terminal stage there are marked alterations in the microscopic picture such as fibrosis, degeneration, focal necrosis, coronary sclerosis, etc., which are not prominent in the stage of compensation. On the other hand, experimental studies on animals are more often carried out in the stage of stable hypertrophy without failure. Furthermore, the age of the experimental animal or individual may play a significant role in altering the microscopic picture

Another major cause for divergent results among investigators is that cardiac hypertrophy of different etiologies has been studied Cardiomegaly may be considered to be an adaptive phenomenon in response to a chronic or repeated increase(s) in contractile force per unit cross-sectional area (stress) of the myocardium with a concomitant increase in oxidative energy expenditure per unit mass per beat. Such a

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situation may exist during repeated muscular exercise for long periods (e.g., athletic training, hard physical labor, etc.). Right ventricular hypertrophy has been noted in the chronic hypoxic hypoxia that prevails in residents at very high altitudes. Also chronic severe anemia is known to be associated with cardiomegaly. Numerous cardiovascular abnormalities or diseases may lead to myocardial hypertrophy. These may be grouped under (1) increased cardiac load (resistance to flow or volume output or both), (2) myocardial disease (acquired or genetic), and (3) disease of coronary arteries. It is reasonable to expect that the various conditions causing these disturbances might have different effects on myocardial metabolism and coronary hemodynamics. In a number of cases, hypertrophy may be due to disturbances in endocrine function which alter myocardial metabolism and cause growth of the organ. Notable among these are excessive secretion of thyroid hormone, growth hormone, and adrenal medullary and cortical hormones. These hormones may act directly on cardiac metabolism and/or indirectly by altering the circulation of blood and thereby cardiac dynamics. Since the metabolic effects of these hormones differ, it is likely that their myocardial metabolic action and coronary dynamics may also be dissimilar. The importance of dietary intake in the development and maintenance of cardiac hypertrophy should be kept in mind.

A third factor contributing to the discrepancies between the results of different investigators is related to the method of evaluating coronary circulation from postmortem studies (injecting coronary vessels, counting the capillaries or arterioles, counting the muscle fibers in cross section, etc.). We shall note below that there is an important difference between the morphologic and the physiologic approach to the study of the coronary circulation in cardiac hypertrophy. Recent physiologic studies do not seem to corroborate the classical view based primarily on anatomic findings which emphasized the inadequacy of the coronary circulation and oxygen supply in advanced stages of pathologic hypertrophy of the heart.

Myocardial circulation in cardiomegaly caused by physical training

Considerable interest centers around this subject in sports medicine with respect to the possible harmful effects of the cardiac hypertrophy commonly seen in athletes. Clinical interest in this problem is related to the possible beneficial effects of moderate exercise on the development of collateral vessels in diseases of the coronary arteries. Hypertrophy of the heart in trained athletes is described as "physiologic." In man the weight of the heart does not exceed the so-called critical value of 500 grams.[3]

Postmortem studies of coronary vessels. Myocardial capillarization has been extensively studied in the hypertrophied heart associated with physical exercise and training. Petrén and co-workers[4,5] induced cardiac hypertrophy in young guinea pigs by repeated exercise and counted the capillaries per square millimeter of cross-sectional area (erythrocyte staining). They reported an increase in the number of capillaries per square millimeter (referred to as capillary concentration or density) in the hypertrophied heart as compared with normal controls. On the other hand, Frank[6] repeated these studies in adult guinea pigs and reported a decrease in capillary concentration in hypertrophied hearts. These contradictory results have been attributed to the difference in the age of the animals. Young animals show a tendency for growth and multiplication of vessels.

In 1955, Hakkila[7] reinvestigated this problem very extensively using three different methods to count the myocardial capillaries. He used three-week-old guinea pigs and exercised them for three and one-half months. He found a significant decrease in the number of capillaries per square millimeter of microscopic field in trained animals as compared with controls. He supported the view that in exercise hypertrophy there is no multiplication of myocardial capillaries. The decrease in capillary concentration he felt is probably due to the increase in the cross-sectional area of the hypertrophied muscle fibers which push the capillaries further apart. Some investigators[8] have compared the capillarization of the relatively large heart of the hare (athletic

animal) with that of the domesticated rabbit (nonathletic animal) in animals of approximately the same body weight. It was noted that the hare had a greater muscle cell concentration per square millimeter (smaller fiber diameter) with a correspondingly greater capillary concentration. One should remember that this difference may be due, at least partly, to genetic factors.

The capacity or size of the coronary arterial system has been studied post mortem in different ways. Tepperman and Pearlman[9] worked out a technique to make a vinyl acetate cast of the coronary arterial tree. Its weight was taken as an index of the size of the arterial system. In chronically exercised rats they noted a statistically significant increase in the coronary cast weight as compared with controls and in some experiments the coronary cast weight to heart weight ratios were significantly increased. These observations were extended and confirmed by Stevenson and co-workers.[10] These investigators concluded that moderate exercise in rats causes an increase in the relative size (volume) of the coronary arterial tree, but they pointed out that this observation does not necessarily indicate an increase in coronary arterial flow in vivo.

Leon and Bloor[11] used the measurement of the cross-sectional areas of the right and left coronary arteries in rats as an estimate of the capacity of the coronary arteries. They exercised rats by subjecting them to swimming and measured the cross section of the coronary arteries at a distance of 0.5 mm from their origin. They also counted the capillaries and myocardial fibers. It was found that the cross-sectional area of both arteries was greater in exercised than in control animals. Likewise the ratio of capillaries to muscle fibers was greater in exercised animals.

Coronary flow in vivo. Although valuable information may be gained from post mortem studies, it has been pointed out by Gregg[12] that such studies may not indicate the coronary flow in vivo. It is most surprising that, despite the availability of methods, studies of the coronary blood flow in trained animals and man have not been carried out to any significant extent.[12] One subject who was a soccer player for a long period was studied by Bolt and co-workers.[14] In this individual left ventricular coronary flow and O_2 consumption per unit mass of tissue was well within normal limits. The nitrous oxide saturation technique was used to measure the coronary flow.[11]

Myocardial circulation in cardiomegaly associated with chronic hypoxia of high altitude

Early radiological observations by Kerwin[6] and Rotta[17] demonstrated that residents of very high altitudes may have enlarged hearts. No autopsy data were available to determine the existence of ventricular hypertrophy. Later experimental and clinical studies[18-21] showed that the cardiac hypertrophy which occurs frequently is essentially limited to the right ventricle. This was explained on the basis of the pulmonary hypertension that often supervenes in hypoxic hypoxia. In acclimated man at high altitudes there is little change in cardiac output or systemic arterial pressure.[22] This may explain the absence of left ventricular hypertrophy. The increase in pulmonary arterial pressure is caused by an increase in pulmonary vascular resistance believed to be due to a direct constrictor effect of low alveolar P_{O_2} on the pulmonary vasculature.

Postmortem studies. Kerr and associates[24,25] have used the low pressure chamber to induce long term hypoxia in rats. They observed cardiac hypertrophy and measured the size (volume) of the coronary arterial system by the vinyl acetate corrosion technique of Tepperman and Pearlman. They reported an increase in the ratio of coronary cast weight to heart weight. It was concluded that the myocardium did not outgrow its blood supply under their experimental conditions.

In vivo studies. Measurement of coronary blood flow in animals and in men residing at high altitudes (or exposed to low pressure for long periods) have not been reported, to the author's knowledge. If the hypertrophy is truly limited to the right ventricle, the N_2O method will provide little information since it determines the flow essentially through the left ventricular myocardium. The newer isotope washout

situation may exist during repeated muscular exercise for long periods (e.g. athletic training, hard physical labor, etc.). Right ventricular hypertrophy has been noted in the chronic hypoxic hypoxia that prevails in residents at very high altitudes. Also chronic severe anemia is known to be associated with cardiomegaly. Numerous cardiovascular abnormalities or diseases may lead to myocardial hypertrophy. These may be grouped under (1) increased cardiac load (resistance to flow or volume output or both), (2) myocardial disease (acquired or genetic), and (3) disease of coronary arteries. It is reasonable to expect that the various conditions causing these disturbances might have different effects on myocardial metabolism and coronary hemodynamics. In a number of cases hypertrophy may be due to disturbances in endocrine function which alter myocardial metabolism and cause growth of the organ. Notable among these are excessive secretion of thyroid hormone, growth hormone, and adrenal medullary and cortical hormones. These hormones may act directly on cardiac metabolism and/or indirectly by altering the circulation of blood and thereby cardiac dynamics. Since the metabolic effects of these hormones differ, it is likely that their myocardial metabolic action and coronary dynamics may also be dissimilar. The importance of dietary intake in the development and maintenance of cardiac hypertrophy should be kept in mind.

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500 grams) the growth of the coronary arteries and ostia is inadequate for the increased mass of myocardium to be supplied. Hence he claims that there exists an insufficient coronary perfusion and defective nutrition of the hypertrophied myocardium leading to focal necrosis and diffuse fibrosis.

Overy and associates[27] induced right ventricular hypertrophy by banding the pulmonary artery in sheep and noted an increase in the diameter of the right coronary artery by postmortem injection and radiographic measurements.

In 1967 Baroldi and Scomazzoni[28] published a very extensive study of human coronary circulation in normal and pathologic hearts by the postmortem injection method. It was noted that in hypertrophied hearts there is a lengthening of the extramural large arteries—said to be proportional to the increase in heart volume. Furthermore there was an increase in the overall mean diameter of these vessels, but the measurements rarely exceeded the upper normal limits. Also there was no close correlation between the increase in diameter of these arteries and the increase in muscle mass. The importance of age could not be assessed. Baroldi reported an increase also in the diameter and length of the intramural arterial system, apparently in proportion to the increase in muscle mass. There was an increase in the diameter and length of anastomotic arterioles in the hypertrophied myocardium. An increase in diameter and length of the venous system draining the hypertrophied myocardium was likewise noted.

In vivo studies. West and co-workers[29] induced arterial hypertension in dogs by the cellophane perinephritis method of Page. Coronary flow in the hypertrophied left ventricle was determined by the N_2O saturation method of Kety and Schmidt in the anesthetized animal. Coronary flow and myocardial oxygen consumption per 100 Gm. left ventricle per minute in the hypertrophied ventricle were not significantly different from normal controls. The heart rates were similar in the two groups. These studies were carried out two to three months after the onset of hypertension and there were no signs of congestive failure. The hypertrophy was in stage two (stable).

On the other hand studies in dogs with aortic insufficiency produced by injuring one or more cusp(s) showed a significant increase in coronary blood flow and oxygen consumption per 100 Gm. per minute.[30] These studies were done 3 to 31 days postoperatively and thus represent hearts which were *undergoing* hypertrophy (first stage). It is known that coronary flow and myocardial oxygen consumption during the first stage of hypertrophy is greater than normal.[31] Besides, the dogs with aortic regurgitation had a distinctly faster heart rate. This is known to increase myocardial oxygen uptake when external work is kept constant.[32]

Studies of coronary flow in man were first carried out by Bing and associates[33] in 1949. The N_2O saturation technique was used to measure left ventricular coronary flow in normal subjects and in patients with various forms of cardiovascular disease. Although the number of cases was few, it was noted in patients with hypertension or congestive failure with radiological evidence of marked left ventricular enlargement that coronary flow and myocardial oxygen consumption per 100 Gm. tissue were not significantly different from normals.

It should be pointed out that to date all measurements of coronary blood flow *in cardiomegaly* have been carried out by the nitrous oxide saturation or desaturation techniques.

Rowe and associates[34,35] studied a number of patients with essential hypertension and noted that the coronary blood flow and myocardial oxygen uptake per unit mass of myocardium were normal. Since the coronary perfusion pressure is higher than normal in this condition, it indicated that the resistance of the coronary system was increased.

Gorlin and associates[36] studied patients with left ventricular hypertrophy due to mitral insufficiency, aortic stenosis, or aortic insufficiency in the absence of failure. Under resting conditions the coronary blood flow and myocardial oxygen uptake were slightly higher than in normal subjects. In patients with muscular subaortic stenosis (obstructive cardiomyopathy) Gorlin and

technique utilizing [85]Kr or [133]Xe injected into the right coronary artery with precordial counting might be used to advantage for this purpose.[16]

Myocardial circulation in cardiomegaly induced by cardiac overload

Either volume overloading or pressure overloading of a cardiac chamber of sufficient duration will induce hypertrophy of that chamber. However, pressure or resistance loading is the *more effective means* and is the most frequently used experimental method for inducing ventricular hypertrophy. Either the aorta or pulmonary artery may be constricted. In some cases renal hypertension has been used to induce left ventricular hypertrophy.

Postmortem studies. Shipley and coworkers[17] induced left ventricular hypertrophy in rabbits by *injuring an aortic cusp.* They noted fewer muscle fibers and fewer capillaries per square millimeter of cross section than in control hearts when the animals were sacrificed two to five and one half months later. The ratio of capillaries to muscle fibers was not different *from normal controls.*

Essentially similar findings were reported by Roberts and Wearn[18] in human autopsy material from normal hearts and from hearts hypertrophied from diverse causes (hypertension, rheumatic heart disease, syphilis, coronary disease). The capillary to muscle fiber ratio in hypertrophy was approximately 1:1, which is the same as *normal.* It was concluded that in cardiac hypertrophy the muscle fibers increase in diameter and the capillaries do not multiply.

More recently, Rakusan and Poupa[19] induced cardiomegaly *in growing rats* by increasing arterial resistance with a silver *ring* around the aorta. They noted a significant decrease in the number of capillaries and the muscle fibers per square millimeter of cross-sectional area compared with normal controls. However, the ratio of capillaries *to muscle fibers* was somewhat increased, suggesting a slight increase *in* the number of capillaries.

Rakušan and associates[20] studied the capacity of *terminal* coronary vascular bed by injecting radio-iodinated albumin intravenously. A sample of left ventricular muscle was frozen soon after injection and the activity after digesting with potassium hydroxide was counted. Cardiomegaly was produced in rabbits by *constricting the* aorta. In adult animals, the total capacity of the terminal vessels remained unchanged despite the hypertrophy of the left ventricle. In other words, there was a decrease in terminal vascular capacity per unit mass of hypertrophied muscle as compared with *normal heart muscle.*

Kountz and Smith[21] revived human hearts post mortem by perfusing the coronaries. Hypertrophied hearts from subjects who died of congestive failure showed a lower coronary flow per gram of muscle than normal hearts. Dock[22] perfused human hearts post mortem with kerosene (non-beating) and reported that the coronary *flow was less per gram of* tissue in hypertrophied hearts than in normal hearts. Vivell[23] perfused atrophic, normal, and hypertrophic human hearts 48 hours after death with a mixture of paraffin and carbon tetrachloride (viscosity close to that of blood) at various perfusion pressures. Over *a considerable range of heart weights* he noted, as had the previous workers, that the coronary flow *(milliliters per gram per* minute) decreased in proportion to the increase in heart weight.

Other investigators[11,25] have attempted to measure the total capacity (luminal *volume) of the coronary arterial tree in* man by postmortem injections and radiological studies to visualize the arteries. They reported that the capacity or size of the arterial tree increases with the weight of the heart, but whether or not this is proportional to the increase in muscle mass was *uncertain.* Woods[24] calculated the cross-sectional area of the right coronary artery at its largest diameter in human autopsy material. He noted that the cross-sectional area of the artery in relation to the mass of muscle supplied was *less than normal.* It was concluded that the hypertrophied myocardium suffers from relative ischemia.

Linzbach[8] from his extensive studies of cardiac hypertrophy expressed the view that in pathological *hypertrophy of* the heart in man (above the critical weight of

oxygen consumption per 100 Gm were significantly increased. In these studies the existence of cardiac hypertrophy was not mentioned. However, it has been reported that about 50 per cent of hyperthyroid patients show cardiac hypertrophy at autopsy.[82]

Olson and Piatnek[41] induced thyrotoxicosis in dogs by feeding thyroid powder daily for two to four months. These animals demonstrated a significant increase in left ventricular coronary flow and myocardial oxygen consumption per 100 Gm. per minute. Cardiac output was markedly increased and all other signs of hyperthyroidism were present. Unfortunately, no data were presented on heart weight in these animals. In another study these investigators[41] reported that cardiomegaly was a constant feature in thyrotoxic dogs.

More recent studies on hyperthyroid patients by Wendt and associates[42] confirmed the early report of Bing. Both the coronary flow and myocardial oxygen consumption per 100 Gm. per minute were within the normal range.

The contradictory findings of different workers on coronary flow in thyrotoxicosis remain unexplained. In these studies the possible influence of heart rate and body temperature on myocardial oxygen uptake has been overlooked.

Myocardial circulation in idiopathic cardiomegaly

Wendt and associates[43] studied a number of patients with idiopathic cardiomegaly. They noted that left ventricular coronary flow was somewhat on the low side but myocardial oxygen uptake per 100 Gm. per minute was well within the normal range.

More recently, Brink and Lewis[44] studied myocardial metabolism in the idiopathic myocardiopathy (idiopathic mural endomyocardiopathy) seen in South Africa. They reported that left ventricular coronary flow and myocardial O_2 uptake per 100 Gm. were within normal limits and that there was no evidence for the occurrence of anaerobic metabolism in the hypertrophied heart under resting conditions. Myocardial uptake of glucose, lactate, pyruvate, and free fatty acids were also found to be normal.

Myocardial circulation in cardiac hypertrophy associated with acromegaly

Excess growth hormone is known to induce cardiac hypertrophy experimentally.[45] Cases of acromegaly without hypertension may demonstrate cardiac hypertrophy.[46] To the author's knowledge, the coronary circulation in acromegalic patients or in animals receiving growth hormone over a period of time has not been investigated.

Discussion

Morphologic studies. From the foregoing presentation it is apparent that coronary circulation in cardiac hypertrophy has been studied more extensively from a morphologic than from a functional standpoint. The reason for this is obviously related to the difficulties of measuring coronary flow in vivo, particularly in small animals which are more convenient to use. The hypertrophy studied has been mostly in stage 2 or 3. The anatomic findings in experimental studies have led to some contradiction depending upon the method of inducing hypertrophy, the age of the animal, the method of assessing the changes, etc. Despite these difficulties the following is an attempt to summarize the results.

Practically all investigators agree that in human and experimental cardiomegaly (not complicated by coronary artery disease) the "capacity" or luminal volume of the coronary arterial tree is increased. This is due to lengthening and widening of the arteries, including the anastomotic vessels.

However, there is disagreement as to the adequacy of the increase in capacity in relation to the increased mass of myocardium. Some authors believe that the proportion remains normal, while others claim that the arterial growth and widening are insufficient for the needs of the increased muscle mass (postulated relative ischemia or hypoxia).

With regard to the structural changes in coronary microvessels there is more divergence of findings, probably because these vessels can grow and multiply more readily than the larger vessels, especially in young animals. It is generally held that in cardiomegaly of adult animals and in man the

co-workers[46] *found normal* coronary flow and myocardial oxygen consumption per 100 Gm. *left ventricular tissue.*

Extensive studies by Blain and associates[47] *in congestive heart failure confirmed* these findings. Similar results were reported by Levine and *Wagman*[48] *on patients with* chronic congestive failure with marked hypertrophy of the ventricle. Blain and associates noted also that the myocardial usage of glucose, pyruvate, fatty acids, amino acids, and ketones was not altered in both compensated heart disease and frank failure.

Rowe and associates[49] studied patients with aortic valve disease. In subjects with aortic stenosis the resting left ventricular coronary flow and myocardial oxygen consumption per 100 Gm. per minute were within the normal range whereas in those with aortic insufficiency the values were *somewhat elevated. During muscular* exercise, in both groups of patients, the coronary blood flow *and myocardial* oxygen uptake increased significantly.

Frank and associates[50] studied myocardial metabolism in subjects with congenital defects (patent ductus arteriosus, ventricular septal defect, coarctation of the aorta) that cause either a pressure or volume overload of the left ventricle and were not in failure. They found that the resting left ventricular coronary flow and myocardial oxygen uptake were significantly higher in the patients *with such defects than in* normal subjects. It is presumed that left ventricular hypertrophy was present in these patients.

Olson and Piatnek[51] induced cardiomegaly with congestive heart failure in dogs by surgical avulsion of the tricuspid valve and stenosis of the pulmonary artery. They found that coronary blood flow and myocardial oxygen uptake in these animals were not different from normal controls.

Studies of *myocardial energetics in acute* and chronic overloading of the heart have led to the view that prolonged increase in contractile stress (force per unit cross-sectional area) increases the energy expenditure of the heart and induces hypertrophy of the myocardium as a compensatory phenomenon. Thickening of the fibers and of the wall of the chamber serves to redistribute the mural force over a larger cross-sectional area of the myocardium thereby restoring the contractile stress and energy expenditure per unit mass of muscle to approximately normal values.[7,44,50-51] It is postulated that the restoration of energy *expenditure per unit mass of muscle* delays the onset of failure and thus prolongs the survival of the organism.

Myocardial circulation in chronic severe anemia with cardiomegaly

Although severe anemia causes a type of volume loading of the heart, it may alter *coronary vascular bed and blood flow* by mechanisms other than changing cardiac dynamics. Hence, *it may* deserve separate treatment.

Iron deficiency (sideropenia) has been used experimentally to induce anemia and cardiomegaly.[57] Poupa and co-workers[53,54] found that cardiomegaly caused by anemia in young rats is associated with a normal number of cardiac muscle cells and capillaries per square millimeter of microscopic field. The cardiomegaly was explained on the basis of multiplication of myocardial cells *(hyperplasia) without increase in the* diameter of the fibers. Apparently, the *capillaries multiplied in proportion* to the muscle cells. These findings may be related to the age of the animals. It is suspected that multiplication of tissue cells is favored in the young.

Early studies of Bing and associates[55] in three *mildly* anemic human subjects showed normal coronary flow and oxygen consumption per unit mass of myocardium. A later report of Bing[56] *on two subjects with severe* anemia indicated that coronary flow is *markedly increased* and oxygen uptake per 100 Gm. per minute is moderately elevated. The presence of cardiac hypertrophy in these cases was not commented upon.

Myocardial circulation in hyperthyroidism

Preliminary studies of Bing[56] reported normal coronary flow in a few patients with hyperthyroidism. The subsequent work of Rowe and co-workers[61] and Leight and associates[62] *on a larger series* indicated that both coronary blood flow and myocardial

with various degrees of narrowing of the coronary arteries and also found no correlation between the coronary flow measurements and the degree of arterial narrowing as rated by their method. These studies support the view that in localized slowly progressive disease of *large* arteries, considerable narrowing of the vessel must occur at any one point before a reduction in flow can be detected. The reason is that the large vessel is a very small fraction of the total resistance of the vascular bed and in *chronic* narrowing of the large vessel there are peripheral vascular changes tending to reduce their resistance. Hence, the total resistance remains practically unaltered until a critical narrowing is reached. The importance of this concept in clinical medicine cannot be overemphasized.

In vivo studies. The foregoing considerations justify the argument that the metabolic adequacy of coronary circulation in cardiomegaly is best studied in the organ in vivo. The advent of the N_2O technique to measure left ventricular coronary flow in large animals (dog, man) has made it possible to obtain more significant data than was possible from postmortem morphologic studies. To be meaningful, comparison of coronary flow between the hypertrophic and the normal myocardium must be made on the basis of unit mass of tissue. Fortunately, the N_2O method (as well as the more recent isotope clearance methods) makes it possible to study myocardial mean blood flow, oxygen consumption, and other metabolic measurements on the basis of *a unit mass of perfused ventricular tissue.* This is particularly valuable in man where comparative data on ventricular muscle mass would not be available in the living state. On the other hand the method lacks some degree of precision. Gregg and coworkers[n] have compared the nitrous oxide method with the direct measurement of coronary flow using the rotameter and noted a variation of ±12.4 per cent. This somewhat limits the usefulness of the method. Other limitations of the N_2O technique have been recently discussed by Klocke and Wittenberg.[n]

Newer methods of measuring coronary flow based on the clearance or washout of radioactive isotopes (^{85}Kr, ^{133}Xe, ^{86}Rb, etc.) injected into one of the coronary arteries provide other avenues of investigation.[n] None of these methods have been applied to the hypertrophied heart in animals or in man. According to Herd and associates[n] and Ross and co-workers[n] the agreement between the ^{85}Kr or ^{133}Xe clearance measurements and direct measurement with the rotameter is good. Moir[n] on the other hand reported that ^{86}Rb clearance underestimates the flow significantly when compared with rotameter flow, whereas Winbury and Gabel[n] claim that ^{86}Rb clearance is a reliable indicator of nutritional circulation of the myocardium. Bassingthwaighte and associates[n] have made a careful study of the isotope washout technique in isolated perfused heart of dogs and discuss the sources of error involved. At present it seems uncertain that the isotope clearance methods are more reliable than the N_2O method.

Based on the N_2O method, the results of most investigators indicate that in cardiomegaly of diverse origins, with or without heart failure, resting left ventricular blood flow and oxygen consumption per unit mass of tissue is within normal limits. In a few instances the values were above normal, but in no case was there a significant reduction in coronary blood flow or myocardial oxygen uptake per unit mass of tissue. This finding raises serious objections to the view that the coronary flow to the hypertrophied myocardium is inadequate and therefore responsible for the onset of failure. Likewise, serious doubts may be raised about the validity of the widely held concept that the hypertrophied cardiac fiber beyond a certain thickness suffers O_2 lack at its central core because of increased diffusion distance.[n]

On the other hand, one might argue that the nitrous oxide method of determining coronary flow being imprecise gives a fairly wide range of normal values.[n] Hence statistical comparisons in different subjects may not detect *minor* degrees of ischemia or hypoxia which *may be* critical in causing *derangements* of myocardial cell metabolism and thus initiating failure.

It must be realized that the N_2O method, which measures the overall blood flow to the left ventricular myocardium, does not indi

ratio of the number of capillaries to the number of muscle fibers is maintained normal (roughly 1 1) Since the muscle fibers increase in diameter the distance between capillaries is correspondingly increased There is evidence that in cardiac hypertrophy the number of sarcomeres per muscle cell is also increased thereby lengthening the fibers.[4, 69, 70] Presumably the capillaries lengthen to keep pace with the increased longitudinal surface of the hypertrophied cells Investigators have paid little attention to this problem although it may be an important consideration in the nutrition of the muscle fibers. In the literature there is little comment about the diameter of the capillaries in cardiac hypertrophy and it may be assumed that there is no significant change According to Linzbach[4] when pathologic hypertrophy in man exceeds a heart weight of about 500 grams there is multiplication of cardiac cells by longitudinal fission This opinion has not been universally accepted and requires further study

Critique of postmortem morphologic studies All too often investigators have drawn far reaching conclusions regarding the adequacy of coronary flow in the living state from postmortem studies of a limited segment of the coronary vascular bed The most frequently studied region has been that of the large coronary arteries It is well known in hemodynamics that the large vessels offer very little resistance to flow as compared with the total resistance of minute vessels. Needless to say the major resistance in a vascular system (excluding viscosity) is offered by the sum total of the small arteries arterioles and the capillaries This is dependent not only on the diameter of these structures but also on their *total number functioning in parallel* and their total length The structural changes in the coronary vascular bed of hypertrophied cardiac muscle may alter these variables in a complex manner and opposing influences may operate. For instance lengthening of a vessel would increase its resistance to flow (resistance α length of tube) whereas increase in its diameter would diminish its resistance (resistance $\alpha \frac{1}{r^4}$) As Baroldi has clearly demonstrated in cardiac hypertrophy the coronary arterial system (both extramural and intramural) lengthens and increases in its mean diameter The net quantitative influence of these changes on flow in the coronary bed is impossible to predict Furthermore quantitative data on the more important resistance vessels (arterioles capillaries) in terms of total length diameter and number are lacking Even if such information were at hand it would be impossible to predict the net effect of such changes on flow

In addition to these postmortem structural changes affecting vascular resistance, one should consider the various physiologic factors affecting resistance to flow in vivo Coronary vessels like others are subject to neurogenic mechanical and chemical influences that alter their diameters and their functional number in the living organism The extramural compression during the cardiac cycle may be altered in diseased states that induce cardiac hypertrophy Metabolites from contracting muscle are known to have a dilator action These chemicals may be altered in hypertrophy with or without failure The recent report of Martini and Honig[71] that not all capillaries in the coronary bed may be open normally brings up the possibility that a decrease in coronary resistance in vivo may be accomplished not only by dilatation of functioning vessels but also by the opening up of nonfunctioning ones. Changes in the neurogenic influences on the coronary vessels in hypertrophy with or without failure remain to be explored

Such considerations support the view that it is futile to estimate the adequacy of coronary flow in hypertrophied myocardium by studying the postmortem features of the coronary vascular bed especially that of the large arteries.[11, 72] In this regard the recent observations of Rowe and associates[73] are pertinent. These investigators attempted to quantify the degree of atherosclerotic narrowing of the major coronary arteries in patients with angina pectoris by means of coronary angiography and at the same time determined the coronary blood flow with the N_2O technique They reported no decrease in coronary blood flow and myocardial oxygen consumption in subjects

with various degrees of narrowing of the coronary arteries and also found no correlation between the coronary flow measurements and the degree of arterial narrowing as rated by their method. These studies support the view that in localized slowly progressive disease of *large* arteries, considerable narrowing of the vessel must occur at any one point before a reduction in flow can be detected. The reason is that the large vessel is a very small fraction of the total resistance of the vascular bed and in chronic narrowing of the large vessel there are peripheral vascular changes tending to reduce their resistance. Hence, the total resistance remains practically unaltered until a critical narrowing is reached. The importance of this concept in clinical medicine cannot be overemphasized.

In vivo studies. The foregoing considerations justify the argument that the metabolic adequacy of coronary circulation in cardiomegaly is best studied in the organ in vivo. The advent of the N_2O technique to measure left ventricular coronary flow in large animals (dog, man) has made it possible to obtain more significant data than was possible from postmortem morphologic studies. To be meaningful, comparison of coronary flow between the hypertrophic and the normal myocardium must be made on the basis of unit mass of tissue. Fortunately, the N_2O method (as well as the more recent isotope clearance methods) makes it possible to study myocardial mean blood flow, oxygen consumption, and other metabolic measurements on the basis *of a unit mass of perfused ventricular tissue.* This is particularly valuable in man where comparative data on ventricular muscle mass would not be available in the living state. On the other hand the method lacks some degree of precision. Gregg and co-workers[17] have compared the nitrous oxide method with the direct measurement of coronary flow using the *rotameter* and noted a variation of ±12.4 per cent. This somewhat limits the usefulness of the method. Other limitations of the N_2O technique have been recently discussed by Klocke and Wittenberg.[23]

Newer methods of measuring coronary flow based on the clearance or washout of radioactive isotopes (^{85}Kr, ^{133}Xe, ^{86}Rb, etc.) injected into one of the coronary arteries provide other avenues of investigation.[24, 25, 26] None of these methods have been applied to the hypertrophied heart in animals or in man. According to Herd and associates[5] and Ross and co-workers[25] the agreement between the ^{85}Kr or ^{133}Xe clearance measurements and direct measurement with the rotameter is good. Mohr[27] on the other hand reported that ^{86}Rb clearance underestimates the flow significantly when compared with rotameter flow, whereas Winbury and Gabel[28] claim that ^{86}Rb clearance is a reliable indicator of nutritional circulation of the myocardium. Bassingthwaighte and associates[29] have made a careful study of the isotope washout technique in isolated perfused heart of dogs and discuss the sources of error involved. At present it seems uncertain that the isotope clearance methods are more reliable than the N_2O method.

Based on the N_2O method, the results of most investigators indicate that in cardiomegaly of diverse origins, with or without heart failure, resting left ventricular blood flow and oxygen consumption per unit mass of tissue is within normal limits. In a few instances the values were above normal, but in no case was there a significant reduction in coronary blood flow or myocardial oxygen uptake per unit mass of tissue. This finding raises serious objections to the view that the coronary flow to the hypertrophied myocardium is inadequate and therefore responsible for the onset of failure. Likewise, serious doubts may be raised about the validity of the widely held concept that the hypertrophied cardiac fiber beyond a certain thickness suffers O_2 lack at its central core because of increased diffusion distance.[22, 30]

On the other hand, one might argue that the nitrous oxide method of determining coronary flow being imprecise gives a fairly wide range of normal values.[11, 12] Hence, statistical comparisons in different subjects may not detect *minor* degrees of ischemia or hypoxia which *may be critical* in causing derangements of myocardial cell metabolism and thus initiating failure.

It must be realized that the N_2O method which measures the overall blood flow to the left ventricular *myocardium* does not indi

cate the distribution of blood to various portions of the muscle According to Honig and co workers[44] normally the deepest layers of the left ventricular myocardium in the dog receive about half the amount of blood perfusing the superficial layers because of the greater extravascular compression during systole The Po_2 in tissue spaces of the deep layers as measured polarographically is lower than that of the superficial layers[44,47] and a relative hypoxia of the deep layers is postulated It is claimed that in hypertrophy of the left ventricle the *increase in diffusion distance to the central* core of the thickened fibers would add its share in making the subendocardial layers more hypoxic and particularly susceptible to ischemic injury and necrosis. If the hypoxia concept were true one would expect some decline in the oxygen consumption of the left ventricle per gram of tissue when the left ventricle is markedly hypertrophied This however is not the case The possibility that reduced O_2 uptake of deeper layers in hypertrophy may be masked by an increase in O_2 uptake of the superficial layers appears unlikely Furthermore the studies of Moir and DeBra[41] do not support the concept of underperfusion of the subendocardial layers in either the normotensive or hypertensive left ventricle as long as the normal coronary perfusion pressure and flow are maintained This controversial problem requires more study

A further theoretical possibility should be considered Although the oxygen uptake of a thickened myocardial fiber per unit mass of tissue may be within the normal range this does not preclude the possibility of a limitation in the transport of other metabolic substrates Likewise there may be a transport limitation of metabolic waste products in the absence of a limitation in the diffusion of carbon dioxide. There may also be disturbances in electrolyte (Na K Ca Mg) transport and the intracellular or sarcotubular concentration of electrolytes. Iseri and associates[49] studied patients with left ventricular hypertrophy without evidence of congestive failure who had received no cardiac glycosides during hospitalization and had died of noncardiac causes They reported that the myocardial concentrations (per 100 Gm wet tissue) of water Na K Cl Mg and phosphorus were almost identical with those of a control group of subjects with normal hearts. Obviously this study suffers from the uncertainties of postmortem biochemical changes. Vihert and Pozdyunina[49] induced left ventricular hypertrophy in rats by constricting the aorta In animals studied two to three months after operation without signs of impaired cardiac function or histological evidence of cardiosclerosis, concentrations of Na and Ca in the myocardium were normal Potassium concentration was about 5 per cent above that of control animals. On the other hand rats with cardiac hypertrophy pronounced cardiosclerosis and some latent signs of failure showed slightly less K (8 per cent less) and more Na and Ca than controls The authors attribute these changes partly to the death of some muscle fibers and their replacement with connective tissue which is known to be rich in Na Both of the foregoing studies suffer from the drawback that concentrations are expressed per wet weight of whole tissue with no attempt to characterize the intracellular concentrations.

It is significant to note that some biochemical derangements other than in electrolytes have been reported in the hypertrophied myocardium before the onset of failure[42] In line with this is the observation by most investigators (with few exceptions) that the contractile capacity or contractile state (as expressed by V_{max}) of a unit mass of nonfailing hypertrophied heart muscle is below that of a unit mass of normal myocardium[11,14] These findings suggest that overt failure in the hypertrophied myocardium does not indicate the beginning of physical and chemical disturbances in the muscle

Several investigators[16,47,48,41] have studied the uptake of glucose lactate pyruvate ketones and fatty acids, in the hypertrophied heart with or without failure The findings have led to the conclusion that the utilization of foodstuffs by the myocardium is not altered in the presence of hypertrophy even with failure

Some have argued that in myocardial hypertrophy despite the normal coronary blood flow and oxygen consumption there may be an increased nutritional demand

per unit mass of muscle tissue and thus a *relative* ischemia may exist. The evidence to date seems to argue against this hypothesis. If it is accepted that contractile tension or stress is one of the important determinants of cardiac oxygen consumption,[95-97] calculation of myocardial stress in the hypertrophied myocardium in man has given values that are within the normal range.[83,98] According to Huckabee[99] the inadequacy of myocardial oxygenation is indicated by a disturbance in the pyruvate-lactate metabolism of the heart. Hypoxia would lead to the accumulation of lactate which readily diffuses into the capillary blood and coronary venous concentration of lactate would exceed the arterial (excess lactate). Patients with cardiac hypertrophy with or without failure, have a normal myocardial uptake of lactate and pyruvate under resting conditions. This would speak against the existence of relative ischemia or hypoxia.

Gudbjarnason and co-workers[97] have used the redox potential difference of the coronary blood as an index of myocardial hypoxia. Normally coronary venous-arterial difference in redox potential is described as being positive. In hypoxia it tends to become negative. Brink and Lewis[98] found normal positive redox potential difference values in idiopathic myocardiopathy under *resting* conditions.

The question must then be asked: What happens to the coronary circulation and myocardial metabolism in patients with cardiomegaly during the physical and mental activity of everyday life? Does the coronary flow increase sufficiently to meet the demands of the myocardium under these circumstances? Is there a relative ischemia of the myocardium? A few studies[49,84] have indicated an increase in coronary flow and myocardial oxygen consumption during exercise in patients with cardiomegaly not unlike that which occurs in normal subjects. Brink[84] found a slight increase in cardiac pyruvate uptake and a fall in the positivity of coronary redox potential difference suggesting that there may be a tendency toward anaerobic metabolism in exercise. However, it would be unwarranted to generalize from these findings and more work on myocardial metabolism in exercise should be carried out in order to answer the question of whether coronary supply is adequate to meet the demands of the hypertrophied muscle.

It is of interest to note that rats with considerable cardiomegaly are less resistant to high altitude hypoxia than are normal animals.[100] This finding does not of course indicate that the hypertrophied heart suffers from mild hypoxia under normal barometric conditions. The plausible interpretation is that the diffusion of oxygen into hypertrophied fibers at reduced arterial P_{O_2} levels is less adequate than the diffusion into cardiac fibers of normal diameter.

Summary

Postmortem studies of physiologic and pathologic cardiomegaly have shown that there is an increase in the capacity of the coronary arterial tree as a result of lengthening and widening of these vessels. In adults the coronary capillaries and arterioles do not seem to multiply and the ratio of capillaries to muscle fibers remains normal. From postmortem morphologic data it is impossible to gauge the adequacy of coronary flow with respect to the metabolic needs of the increased heart muscle mass.

Based on the N_2O method coronary blood flow and oxygen uptake per *unit mass* of hypertrophied myocardium in the resting dog and man are normal except in some cases of thyrotoxicosis, severe anemia, and aortic insufficiency in which the values were above normal. In no case was the coronary flow or oxygen consumption below normal thereby challenging the classical concept of ischemia or hypoxia as the primary cause of failure of the hypertrophied myocardium. The lack of precision of the N_2O method was pointed out and the possibility of minor degrees of ischemia that may be critical was considered. Possible limitation in the diffusion of nutrients and metabolites (other than O_2 and CO_2) as the basis for metabolic derangements of the thickened myocardial fiber was emphasized.

The concept of relative ischemia or hypoxia due to increased metabolic demand of the hypertrophied myocardium under resting conditions was not supported by available evidence. The importance of considering the adequacy of coronary flow

during physical and mental activity of subjects with cardiomegaly was pointed out.

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Fundamentals of clinical cardiology

Aortic insufficiency
Clinical manifestations and surgical treatment

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The classical clinical pathologic correlation of aortic insufficiency was first presented by Corrigan in 1823.[1] Subsequent to this interest was primarily directed toward differentiating the various causes of valvular incompetence. Table I summarizes the causes of aortic regurgitation. Those more commonly responsible for this hemodynamic abnormality consist of rheumatic fever, syphilis, bacterial endocarditis, aortic root aneurysm, and aortic dissection.

Incompetence of the aortic valve is due chiefly to rheumatic fever. The incidence of severe rheumatic aortic insufficiency in a series of 1,322 patients studied was 6.5 per cent.[2] It occurs chiefly in males in contrast to the greater frequency of mitral stenosis in females. The valve becomes insufficient because of shortened cusps, improper coaptation, and dilatation of the ring. This mechanism, however, varies depending upon the etiology and will be further discussed in relation to the specific underlying condition capable of rendering the aortic valve incompetent.

Moderately severe rheumatic aortic insufficiency may be present with no evidence of cardiac decompensation or disability for as long as two or three decades. Once symptoms of failure or angina pectoris develop, however, the patient's course is downhill and surgical treatment is indicated. Patients with rheumatic aortic insufficiency who present with angina pectoris at postmortem examination or preoperative evaluation show no evidence of coronary artery disease. Angina pectoris, therefore, may be explained by other mechanisms such as marked lowering of diastolic pressure, the sucking action of the regurgitant stream on the coronary arteries (Bernoulli's phenomenon), and disproportionate left ventricular mass to the available arterial supply. Approximately five per cent of the patients with severe aortic regurgitation and fairly well compensated die suddenly and unexpectedly. It has been thought that death is due to acute left ventricular failure or paroxysmal ventricular fibrillation. In general, the association of angina pectoris with congestive failure bears a grave prognosis.

The most significant physical findings are the low diastolic pressure, water hammer pulsation of the peripheral arteries, a blowing decrescendo diastolic murmur, and not infrequently an Austin Flint rumble. Significant left ventricular enlargement is the characteristic feature of long-standing aortic insufficiency. An aortic systolic murmur often associated with a

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thrill is present in all patients with marked aortic regurgitation. The general rule, however, is that the presence of severe aortic insufficiency usually precludes the existence of hemodynamically significant aortic stenosis.

The textbooks on heart disease contain excellent and comprehensive information pertaining to rheumatic and syphilitic aortic insufficiency. In this report the greater space will be devoted to the description of aortic insufficiency caused by less common causes such as rupture of an otherwise normal aortic valve, aortic root aneurysm, aortic dissection, and bacterial endocarditis. The reasons for this emphasis are twofold: (1) the increasing number of patients with the latter conditions requiring medical-surgical treatment and (2) the graver prognosis of this hemodynamic abnormality associated with the latter etiologic factors.

Table I. Aortic insufficiency: Etiology

1. Rheumatic
2. Syphilitic
3. Bacterial endocarditis
4. Aortic root abnormalities
   a. Aneurysm (cystic medionecrotic, arteriosclerotic, syphilitic, giant cell aortitis)
   b. Dissection
5. Rupture of normal valve
   a. Traumatic
   b. Due to strain
   c. Spontaneous
6. Congenital
   a. Perforation or rupture
   b. Bicuspid valve
   c. Sinus of Valsalva aneurysm and/or rupture
   d. Cusp prolapse associated with ventricular septal defect
7. Less common causes
   a. Rheumatoid arthritis (spondylitis)
   b. Reiter's disease
   c. Osteogenesis imperfecta
   d. Ehlers-Danlos syndrome
   e. Mucopolysaccharidosis

Rupture of an otherwise normal aortic valve

Since the first report of rupture of the aortic valve by Henderleath[3] in 1830, approximately 130 additional cases have appeared in the literature.[4-7] The rupture may occur as a result of trauma, strain, or infection; occasionally it occurs spontaneously. It constitutes the valvular lesion most frequently observed in patients who survive nonpenetrating injury. The most common site of rupture is the base of the aorta, then rupture of the cusp itself, and last the detachment of the cusps or commissures from the aortic wall. The feature common to untreated massive aortic insufficiency resulting from rupture, regardless of its etiology, is a grave prognosis. Therefore, early recognition of rupture of the valve as the cause of aortic incompetence is mandatory. The preoperative diagnosis is based on the patient's history, normal heart findings on a recent examination, sudden onset of aortic insufficiency after the accident, and exclusion of other causes of aortic regurgitation. In our experience four out of five patients had the typical musical diastolic murmur with the "sea gull" sound. None, however, had the excruciating chest pain described in many of the reported cases. More interesting and pathognomonic has been a diastolic thrill palpable at the base of the neck. This sign first described by the author[7] is unique to the valve rupture and is found at operation to be due to tremendous vibration of the aortic arch during diastole. The clinical course is that of progressive heart failure intractable to medical management. The decision to operate on these patients is based on the unfavorable course of the disease and predictable good operative results. The procedure of choice is prosthetic valve replacement. Table II summarizes the clinical data in five such patients treated.

Aortic insufficiency secondary to aortic root aneurysm

Aortic root aneurysm usually results in the death of the patient unless treated surgically. Death is invariably due to rupture, occlusion of vital arteries, or congestive heart failure secondary to aortic regurgitation. Almost every patient is symptomatic by virtue of the latter complication.

In evaluating the etiology of the aneurysm three important entities, mainly cystic medionecrosis, syphilis, and arterio-

Table II Aortic insufficiency secondary to rupture of otherwise normal aortic valve

No	Age sex	Cause	Operative findings	Operation	Results
1	62 M	Automobile accident	Commissural detachments, cusp perforation	Starr Edwards aortic valve replacement	Excellent
2	53 M	Strain	Cusp tear and perforations	Starr Edwards aortic valve replacement	Excellent
3	14 M	Fall	Aortic root false aneurysm and partial detachment of valve annulus	(1) Aneurysmorrhaphy and Starr Edwards aortic valve replacement (2) repair of periprosthetic leak	Excellent
4	65 M	Spontaneous	Cusp tear	Valvuloplasty	Asymptomatic residual aortic insufficiency
5	52 M	Blunt trauma	Cusp tear and perforation	Starr Edwards aortic valve replacement	Died of infection 8 mo. after operation

sclerosis have been encountered Cystic medionecrosis the most common cause of aortic root aneurysm is a degenerative noninflammatory process involving most commonly the ascending aorta The aneurysm usually fusiform develops as a consequence of focal degeneration of the elastic matrix of the media Since the tunica intima does not dilate along with the media an intimal rent occurs which results in dissection Some of these aneurysms are the result of an inherited defect as seen in Marfan's syndrome and others are the result of what seems to be an acquired etiological process termed idiopathic cystic medionecrosis. Second to rupture the most important associated hemodynamic abnormality is aortic regurgitation The vast majority of those who develop rupture die before therapy can be instituted Consequently aortic insufficiency has been the most common clinical manifestation leading to the diagnosis of aortic root aneurysm As the importance of aortic insufficiency in these patients has become evident, a variety of surgical procedures—ranging from bicuspidization valvuloplasty and cusp replacement to total prosthetic replacement of the valve—has developed With the availability of reliable prosthetic valves and the speed with which the valve can easily be replaced under these circumstances this procedure has become relatively routine [8, 11] The exception is the patient in whom the insufficiency is due to dissection and downward displacement of one or more aortic cusps. If the cusps are otherwise normal and the valve ring is not dilated circumferential suturing of the dissected layers may completely eliminate the regurgitation Heart surgeons have become increasingly confident in replacing both the ascending aorta and the valve with the appropriate prostheses. This aggressive approach is the treatment of choice and offers maximum protection for the patient's life The following case report is a typical example of a patient with massive aortic regurgitation secondary to an aortic root aneurysm

Case report A 49-year-old Caucasian man was admitted to the hospital in 1965 in congestive heart failure. He was treated successfully and discharged with a diagnosis of ascending aortic aneurysm and aortic insufficiency The second episode of heart failure in spite of medical management led to his readmission to the hospital. The blood pressure at this time was 140/0 The chest roentgenogram showed cardiomegaly marked left ventricular enlargement, and aneurysmal ascending aorta (Fig 1 A) A retrograde aortic root injection of contrast medium revealed a large aneurysm of the ascending aorta and regurgitation of the dye into the left ventricle (Fig 2 A)

The patient was operated upon on Sept. 2, 1965 The aneurysm occupied the entire anterior mediastinum. Because of the likelihood of impending rupture due to the friability of the aortic wall, the femoral vein and artery were cannulated in preparation for partial bypass before any dissection was carried out in the mediastinum. When the aneurysmal ascending aorta was entered it was noted that the dilated annulus was the major cause of valvular



1 A Preoperative chest roentgenogram shows cardiomegaly left ventricular enlargement, and aneurysmal ...ding aorta. *B* Chest roentgenogram taken four years after operation shows marked improvement.

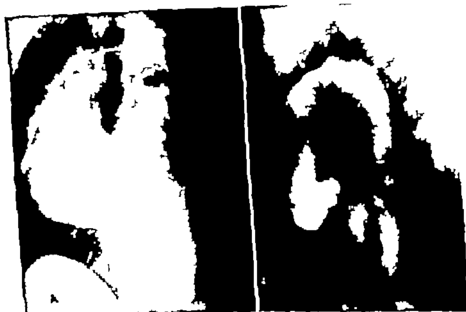


Fig. *2 A* Preoperative aortogram shows large ascending aortic aneurysm with regurgitation of the dye int the left ventricle. *B* Aortogram two months after operation shows normal aortic arch and no regurgitation.

Incompetence A 31 mm. Gott Dagget aortic prosthesis was sutured to the aortic ring after the cusps ere removed. This was followed by resection of the aneurysm and Dacron graft replacement of the proximal aortic arch. The proximal anastomosis was made first. The poor quality of the aortic root, particularly in medionecrotic neurysm, demands meticulous suturing hich is best accomplished by reconstructing the proximal anastomosis first. The postoperative course was entirely uneventful. Retrograde aortogram performed several months after the operation showed normal aortic arch with no evidence of aortic insufficiency (Fig. 2, *B*). This asymptomatic patient with normal heart size is now five years after the operation (Fig. 1 *B*) and has not had any thromboembolic complications. This is mentioned because of the thrombogenicity of the Gott Dagget aortic prosthesis. This valve was utilized only for short period in 1965 and since that time the Starr-Edwards aortic prosthesis has been our preferred aortic valve substitute under these circumstances.

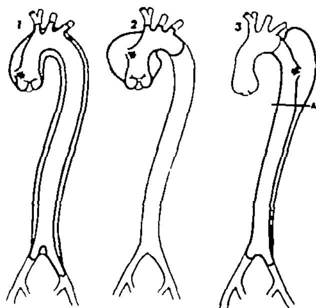


Fig. 3 The three classical types of aortic dissection (From De Bakey, M. D., et al.: J. Cardiovasc. Surg. (Torino) 5:200, 1964; published by Edizioni Minerva Medica. Reproduced by permission.)

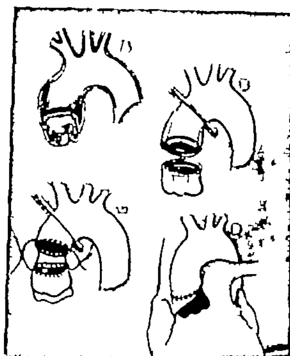


Fig. 4. The schematic drawings of ascending aortic dissection and its surgical repair.

Aortic insufficiency secondary to dissection of the ascending aorta

Untreated dissection of the proximal aortic arch is invariably fatal. Fortunately, the majority of the patients live long enough for diagnosis to be established and therapy instituted.[11] The most common pathologic process leading to spontaneous dissection has been cystic medionecrosis. The inevitable death is usually due to rupture, occlusion of vital arteries, or aortic regurgitation. Aortic dissection should be considered in every patient suffering from acute unexplained chest pain. The widening of the superior mediastinum should arouse a strong suspicion and, in the absence of myocardial damage, retrograde aortography can be accomplished safely to confirm the diagnosis. The presence of aortic regurgitation and/or coronary artery involvement should encourage surgery since a death rate of over 70 per cent due to rupture has been reported in this particular group. Retrograde dissection into the sinus of Valsalva displaces the cusps and produces valvular incompetence. This mechanism differs from dilatation of the valve ring which is responsible for aortic insufficiency in the majority of patients with aortic root aneurysm.

The surgical implication of the mechanism becomes important because displacement of the cusps with normal-sized annulus lends itself to primary repair. In contrast, valve replacement is carried out with increasing frequency when the insufficiency is primarily due to dilatation; reconstruction of the aortic wall with elevation of the dissected intima brings the prolapsed cusps into their normal positions, which in turn restores valvular competence. The following case reports are typical examples of types I and II acute aortic dissection causing massive aortic regurgitation (Fig. 3).[12]

A case of type II aortic dissection. This patient was a 41-year-old man who had been in excellent health until three days prior to admission to another hospital. With a diagnosis of free aortic regurgitation and left heart failure unresponsive to medical therapy, he was transferred to our service for surgical consideration. The patient, nearly comatose, expectorating frothy fluid, severely cyanotic, and with unobtainable blood pressure, was rushed to the operating room where, following minimal skin preparation and rapid draping, connections were made between the right common femoral vessels and the pump oxygenator primed with lactated Ringer's solution as rapidly as possible. Institution of partial bypass was followed by induction of anesthesia, endotracheal intubation, and exposure of the heart via a midline sternotomy incision. The pericardium contained approximately 500 ml. of blood. This was evacuated and a second venous catheter was placed into the right atrium. The ascending aorta

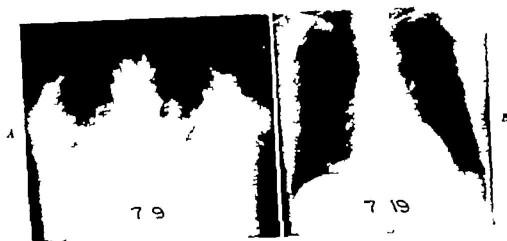


Fig. 5 Anteroposterior roentgenograms. *A* On admission, showing cardiomegaly and massive pulmonary edema. *B* On discharge 10 days after operation, showing significant decrease in heart size and clear lung fields.

was ecchymotic when it was entered, circumferential intimal tear was found typically about one inch superior to the aortic valve. The normal aortic cusps were prolapsed into the left ventricle. Reconstruction consisted of circumferential suturing of the dissected layers and reanastomosis of the divided ends of the aorta (Fig. 4). This resulted in elevation of the prolapsed cusps into their normal positions, thereby restoring valvular competence. The patient maintained an uneventful postoperative course and left the hospital in excellent condition. Fig. 5 illustrates this patient immediate preoperative and ten days postoperative chest roentgenograms. The four year postoperative evaluation has revealed an asymptomatic individual with no evidence of aortic insufficiency.

A case of type I aortic dissection. This 49-year-old man suffered an excruciating substernal and interscapular chest pain shortly after he lifted bag of cement. As the pain subsided he experienced traveling type of discomfort down into his abdomen ending in severe weakness, coldness, and pain in the left leg. Examination revealed findings of aortic regurgitation and pulseless left lower extremity. The diagnosis of dissection was certain on the basis of history and physical findings. The extent of the dissection was precise because of the involvement of the aortic valve and the left iliac artery. It was felt that the dissection typically had resulted from an intimal tear superior to the aortic valve. The absence of left leg pulses indicated no re-entry nd therefore permitted perfusion via a catheter in the right common femoral artery. In the presence of a second tear distally retrograde perfusion will result in massive dissection and is almost never associated with successful outcome. Surgical approach was similar to that described in the previous case. The corrective operation in this case, however consisted of resection of the ascending aorta because of extremely thin outer layer repair of the dissected layers hich proximally resulted in the elevation of the prolapsed aortic cusps to their normal position, and reconstruction of the ascending aorta with the use of Dacron tube prosthesis. An aortic root injection of contrast medium six months after the operation showed competent aortic valve and a stable thoracoabdominal dissection (Fig. 6).



Fig. 6 Four months postoperative aortic root injection of contrast media showing the ascending aortic graft in place (between arrows) competent aortic valve, and stable distal dissection.

Aortic insufficiency secondary to bacterial endocarditis

In the majority of these patients endocarditis is the primary cause of valve de-

struction. Indication for operation in this group primarily consists of congestive heart failure secondary to marked valvular incompetence. An occasional patient is operated upon because of uncontrollable infection. Removal of the infected aortic cusps considered the nidus for persistent bacteremia and positive blood cultures has in many instances been associated with successful outcome. Embolic manifestations, although not uncommon, have rarely been the major indication for aortic valve replacement. The operative findings are those of vegetations in the majority, loss of valve substance, tear or fenestration of the cusps, and seldom perforation of the ventricular septum. The result of operation in this group is generally gratifying.[14]

As in the group with rupture of the valve, the course of aortic insufficiency in these patients not infrequently is downhill; in a few instances emergency replacement of the valve is needed. The important aspect of the surgical treatment if the patient is seriously ill with a precarious cardiac condition is the use of assisted circulation during the most critical period—mainly the interval between the induction of anesthesia and institution of total cardiopulmonary bypass.[15] Before the application of emergency surgery it is important to be certain that (1) maximum efforts utilized to treat the patient medically have failed, (2) the cause of intractable cardiovascular collapse is amenable to surgical repair, and (3) the intended operation can be executed in a manner most likely to succeed in salvaging the patient's life. Under these dire circumstances extensive preoperative evaluation such as cardiac catheterization and angiocardiography should be avoided. When a clinical diagnosis is certain, operation can be undertaken promptly.

Discussion

Surgical treatment of aortic regurgitation was generally unsatisfactory until Hufnagle and associates[16] placed a rigid prosthetic plastic ball valve in the descending aorta just beyond the left subclavian artery, thus preventing about 75 per cent of the regurgitant blood flow. This was followed by other techniques such as bicuspidization of the valve, adding substance, or replacing the leaflet, generally with poor results. Total prosthetic replacement of the valve has become the most commonly applied operation for aortic insufficiency.[17] Favorable results have also been reported with the use of aortic homografts.[18, 19] The valve is inserted with the aid of cardiopulmonary bypass. The approach is through a median sternotomy. Venous return into the oxygenator is by free drainage and may be affected by a single catheter in the right atrium or catheters in the superior and inferior venae cavae. The arterial return is accomplished by roller pump via a cannula in the femoral artery or the distal ascending aorta. The perfusion is maintained at the rate of 2 to 2.5 L. per minute per square meter of body surface area. Both coronary arteries are cannulated and individually perfused by separate pumps with oxygenated blood, which may be normothermic or hypothermic. A drainage catheter connected with the intracardiac suction is inserted into the left ventricle through the stab wound at the apex of the heart. Subsequent to successful replacement of the aortic valve there is generally an alleviation of symptoms, reduction in cardiac size, increased tolerance, and for most patients a return to normal activity. The operative mortality rate usually ranges below 10 per cent and has been as low as no deaths in a group of 100 patients undergoing aortic valve replacement.[20] The postoperative complications include mental disturbances, supraventricular and ventricular arrhythmias, respiratory complications, myocardial infarction, and heart block. Late complications consist of thromboembolic manifestations, endocarditis, recurrent insufficiency due to periprosthetic disruption or ball variant, and hemolytic anemia.

The spectrum of aortic regurgitation is so broad in respect to the severity and varied etiology that the prognosis must virtually be individualized. Rheumatic aortic insufficiency is associated with a better prognosis than the syphilitic type or that due to bacterial endocarditis, aortic root abnormalities, trauma, or the one as

sociated with congenital heart disease. When there is gross cardiac enlargement and electrocardiographic evidence of marked cardiac hypertrophy with S-T segment depression and T-wave inversion there is considerable and unpredictable danger of sudden death even in the absence of significant symptoms or disability. With the development of angina pectoris or congestive heart failure, the outlook becomes progressively more menacing. Nevertheless, operation is still reserved only for patients with severe aortic regurgitation and left heart failure angina pectoris or significant limitation of functional capacity with medical therapy. When angina pectoris is the indication for operation, particularly in older individuals coronary angiography should be performed to exclude associated coronary artery disease. Coronary artery disease may be an indication for additional operative procedures directed toward the relief of obstruction in the major coronary arteries. The indication for aortic valve replacement will be greatly extended in the future as the operative mortality rate and postoperative complications are progressively lowered and better techniques and more superior prosthetic devices are devised.

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Julian Frieden

Direct current cardioversion

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Since its introduction by Lown in 1962 direct current cardioversion has been widely utilized for the correction of many cardiac arrhythmias. Because of the efficacy of the method, the ease of performance, the rapidity with which results are obtained, and the wide margin of safety associated with the procedure, cardioversion has become the treatment of choice in many instances in which antiarrhythmic drugs were previously employed.

Indications and technique

Cardioversion is the most effective therapy available for the immediate conversion of ventricular tachycardia and in the elective treatment of both acute and chronic atrial flutter and fibrillation. Its value in the management of atrial or nodal tachycardia is less evident. Although the many different models of machines of various manufacture differ from each other in the waveform and duration of the electrical discharge, the basic methods of use are similar. In general, the patient's electrocardiogram (ECG) is displayed on an oscilloscope for continuous monitoring. The ECG is used to activate a synchronizing circuit which causes the actual cardioversion discharge to occur within 20 msec. of the peak of the R wave. By preventing the discharge from falling in the "vulnerable zone" of the T wave in this manner, repetitive ventricular discharge which might culminate in ventricular tachycardia or fibrillation is averted. In the emergency treatment of ventricular tachycardia or fibrillation, the synchronizing circuit is not employed and the cardioverting shock may fall at any time.

For the treatment of atrial flutter a 50 watt second (w/s) shock is generally used in this laboratory. Smaller shocks, though effective at times, often result in the development of atrial fibrillation and *are not recommended*. Atrial fibrillation is treated with a 200 w/s shock. If this is unsuccessful, 300 and 400 w/s shocks are employed. Ventricular tachycardia or fibrillation is treated in a similar fashion. Whenever possible, the electrodes are placed on the anterior left thorax over the heart, and directly opposite on the posterior thoracic wall. It has been suggested by several groups that this results in the use of smaller shocks than the conventional method of application.

Anesthesia

Since 1966 intravenous diazepam (Valium) has achieved a wide degree of acceptance for use in cardioversion. In our laboratory, diazepam is administered in 5 mg increments every 4 to 5 minutes up to a maximum of 25 mg. Either somnolence, loss of cutaneous pain sensation, or loss of

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coordinated ocular movement is considered an indication that enough diazepam has been administered With the use of these criteria, the patient will have amnesia for the cardioversion. In general the effects of diazepam are dissipated within 20 minutes and no postanesthetic complications ensue. It has been our experience that patients who have been receiving large amounts of sedation tranquilizers, or analgesics prior to cardioversion require the largest amounts of diazepam. Similarly alcoholic patients have a high requirement to achieve a satisfactory degree of sedation. The policy in our laboratory is that no more than 25 mg of diazepam is administered If this is ineffective small doses of morphine sulfate are administered intravenously With this method it has not been necessary to request the services of an anesthesiologist.

Indications and contraindications

The likelihood of conversion to sinus rhythm in instances where atrial flutter or fibrillation has been present less than one year has been reported to be approximately 90 per cent. In patients who have had the arrhythmia for longer than two years the chance of success decreases to less than 75 per cent. Similarly 25 per cent of patients with the shorter duration of fibrillation maintained the sinus rhythm at the end of two years, as opposed to 10 per cent of those with more chronic fibrillation Accordingly it is our policy to reserve elective cardioversion for those patients whose arrhythmia is of less than one year's duration. Other contraindications include a patient's failure to maintain sinus rhythm after previous conversion patients who are in the immediate pre- or postoperative (cardiac) state, patients with recent embolization, and those with giant left atria. If cardioversion is to be performed after cardiac surgery at least three weeks should be allowed to elapse It is of interest to note that following mitral valve surgery cardioversion resulted in maintenance of sinus rhythm in only 9 per cent of patients who had atrial fibrillation preoperatively By contrast, when atrial fibrillation appeared initially in the postoperative period sinus rhythm was maintained in 82 per cent of the patients two years after conversion. Atrioventricular nodal block, manifested by a slow ventricular response without digitalis, is a further contraindication.

Antiarrhythmic drugs

Many investigators have shown that cardioversion of the patient who is receiving digitalis results in a significantly high incidence of serious ventricular arrhythmias. These have ranged from premature ventricular contractions to ventricular tachycardia and fibrillation. It is the policy of the author to discontinue *short-acting* glycosides three days prior to cardioversion and longer-acting preparations are discontinued one week in advance. If there is evidence of nodal rhythm manifested by regularization of the ventricular response group beating or Wenckebach periods, cardioversion is postponed Similarly cardioversion is not attempted when ventricular tachycardia is thought to be secondary to digitalis toxicity

The use of quinidine or procaine amide in the pre- and postconversion management remains a controversial subject. Several authors have described a greater frequency of persistent sinus rhythm in the patient maintained on suppressive therapy[3] while others have been unable to confirm this. In addition so-called "quinidine syncope, which is in reality paroxysmal ventricular tachycardia and fibrillation occurs with a low frequency in patients treated with even relatively small doses of quinidine. Because of the minor degree of improvement in results and the possibility of fatal, toxic reactions the use of quinidine is not recommended by the author

Anticoagulants

Drawing on past experience obtained with quinidine and procaine amide most groups do not use anticoagulant therapy prior to conversion. However in a large series from Norway[4] emboli occurred in 11 of 209 (5 per cent) patients not given anticoagulants and in only 2 of 228 patients treated with anticoagulants (1 per cent) It has been our policy that only patients with previous emboli are given anticoagulants, beginning three weeks prior to conversion and maintained indefinitely there

after Furthermore embolization within the previous three months should be considered a contraindication to cardioversion without intervening mitral valve surgery

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Annotations

Strokes and hypertension

Epidemiological studies have shown that the incidence of major strokes in hypertensive population is twice that of normotensive one, and other reports[1-3] suggest that if hypertensive patients are adequately treated by hypotensive drugs, the stroke incidence in later life is lessened. It is, therefore, surprising how much controversy persists regarding the treatment of hypertensive patients who have survived a stroke, because if the first two premises are correct it should logically follow that control of hypertension in these patients is beneficial. One school[4] suggests that hypertensive stroke survivors do as well as normotensive, but this work may be criticised on the ground that only geriatric patients were considered, that the highest single blood pressure recording was accepted as evidence of persisting hypertension, and that quite high proportion of patients were omitted from the study. In addition the theoretical objection has been put forward that hypotensive therapy will reduce cerebral blood flow and that transient cerebral ischaemic attacks or major and minor strokes will occur as direct result of lowering blood pressure. Other workers[1-3] have noted the bad prognostic influence of hypertension in patients who have had stroke, a word which by definition includes both cerebral haemorrhage and cerebral infarction. There is, of course, complete agreement that the few hypertensive survivors of intracerebral hemorrhage need hypertensive therapy so that the major controversy is about the management of patients after cerebral infarction.

A prospective trial was, therefore, begun by the author in 1964 and continued for 4 years to find out whether the prognosis of hypertensive patients surviving nonembolic cerebral infarction could be improved regarding morbidity and mortality by adequate hypotensive therapy and whether there was evidence that focal cerebral ischemic attacks or permanent neurological deficits occur when blood pressure is lowered in these patients to normotensive levels.

The series consisted of 104 hypertensive patients out of 244 patients surviving stroke, admitted to the Ashford Hospital, Middlesex, England, in the 4 relevant years. Five patients were excluded on the grounds that hypotensive therapy was obligatory in their case and the remaining 99 were placed at random in treated and untreated groups. Two patients have been lost to follow-up, so that 49 were left in the treated group and 48 in the untreated, and these were followed up from 2 to 6 years. The crude mortality rate in the untreated was 46 per cent compared with 26 per cent in the treated, and this latter figure improved to 17 per cent if only well controlled patients (40 out of 49) were considered. This was significant to the one in a hundred level ($p = .01$)

On dividing the type of hypertension into systolic (systolic blood pressure above 160 mm. Hg) and diastolic (diastolic blood pressure 110 mm. Hg or above) the figures were 7 per cent mortality for well controlled systolic hypertensive patients compared with 37 per cent untreated, and 13 per cent mortality for well controlled diastolic hypertensive patients compared with 52 per cent untreated.

Recurrences were also less in the treated than untreated, 20 per cent compared with 44 per cent, and the striking feature was that out of 13 deaths in the treated group, only one was due to further cerebral infarction, whereas 7 out of 22 deaths in the untreated group were due to this. If, however, only patients over 65 years of age were considered, it was clear that treatment made only a marginal difference to mortality and morbidity rates.

Hypotensive therapy used in this series comprised restriction of salt, control of obesity thiazide diuretic therapy methyldopa, and bethanidine or debrisoquine. Side effects occurred in just over a third of the patients, and postural hypotension was troublesome only in the early stages of treatment, although exertion after change of position was commoner cause than simple change from lying or sitting to standing. The importance of exertion as the major cause of severe hypotensive attacks usually has not been stressed sufficiently in other studies.

With regard to focal cerebral ischemic attacks, none occurred in the carotid territory and there were only two doubtful ones in the vertebro-basilar. These two patients complained of vertigo, instability and dimness of vision, and it is difficult to say whether these were early symptoms of syncope or true focal hind brain ischemic episodes. Similarly no permanent sequelae or disability occurred, as far as could be ascertained, from hypotensive attacks.

It appears from this study that adequate hypotensive therapy has significantly improved the prognosis of hypertensive patients below the age of 65 who survived a stroke. Fears concerning the effects on cerebral blood flow of reducing hypertension proved groundless in this series as no clear cut focal ischemic attacks nor episodes of cerebral infarction occurred as a result of this procedure. Smooth effective control is very important; to obtain good results, as much personal trouble must be taken with hypotensive therapy as with anticoagulant therapy. Enthusiasm and perseverance are essential in the physician undertaking this work, as well as qualities of leadership and dedication, because if

some of his personality does not "rub off" onto the patient to sustain morale the results will be bad. A poorly treated hypertensive patient will probably fare worse than one untreated. Personal care by the same physician is also of importance as the greatest advantage a long term patient can have is to be treated by a familiar figure in familiar surroundings.

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Elastic compression of the lower limbs
Merits and hazards

Venous stasis in the lower limbs has long been considered a significant factor in the causation of thromboembolism in the confined patient. Over the years several modalities with external compression of the limb as their common denominator have been advocated to cope with this potential hazard.[1-3] To critically gauge the value of these measures, the author undertook venous hemodynamic studies and phlebograms of the lower limbs in 156 hospital patients with and without elastic compression of various types.[4,5] These included four groups: 35 patients with varicose veins, 35 patients with acute phlebitis, 40 patients with postphlebitic disease, and 40 normal control patients.

The findings were consistent and reproducible for each group. Compression of the limb with elastic bandages, stockings, or pneumatic splints is effective in significantly reducing the total cross sectional area of the venous pool of the leg, especially in patients with varicose veins (Table I). The optimum external compression pressure (all types) providing maximum reduction of stasis without hemodynamic adversity is between 15 to 20 mm. Hg.[5] Above this level compression effects elevation of the peripheral venous pressure and morphologic evidence of venous occlusion. Bandaging the knee joint (as in post-operative knee surgery) carries the potential of occluding the popliteal vein and greatly increasing the peripheral venous pressure. The pneumatic splint appears ideally suited for this purpose al-

Table I. Peripheral venous pressure with knee high compression*

Patient groups	Supine		Standing*	Ambulatory†	
	Without compression	With compression	With or without compression	Without compression	With compression
Control	8 3	8 9	121 ± 11	48 ± 12	47 ± 10
Varicose veins	10 3	10 4	119 ± 7	67 ± 15	61 ± 16
Phlebitis	22 0	24 5	121 ± 7	123 ± 25	131 ± 22
Postphlebitic	16 2	16 2	123 ± 6	114 ± 22	116 ± 18

*Mean pressure in centimeters of saline ± standard deviation.
†Ambulatory pressure should drop to at least 50 per cent of the standing pressure in normal people.

though it is not practical for active ambulation. Of the modalities evaluated, the knee high graduated pressure stocking* appears to be the choice to combat stasis in the hospital patient.

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ECHO viruses, carditis and acute pleurodynia

The significant role played by enteroviruses, especially those of the Coxsackie group, in acute cardiac disease and pleurodynia at all ages is now well established and has been the subject of recent publications.[1-4] In contrast, there is limited evidence relating the ECHO virus group to these diseases, despite the fact that these viruses do not require sophisticated laboratory techniques for their isolation. Reports that certain types of ECHO virus can, like Coxsackie viruses, cause myositis in newborn mice raised the question whether these and perhaps other types might share Coxsackie-type pathogenicity for man, including causation of acute pleurodynia or acute myopericarditis.

This hypothesis was tested by an analysis of the clinical diagnoses of 833 patients from whom ECHO viruses were isolated in Glasgow, Scotland. ECHO viruses of types 6, 11, 12, 19, and 25 were associated with pleurodynia and/or cardiac disease, and statistical analysis showed a significant excess of pleurodynia, though not of cardiac disease, in the ECHO 6 group and a strongly suggestive association of these

Table I. ECHO virus infections in cardiac disease

Patient No.	Reference	Virology			Age (yr.)	Sex	Illness
		Type	Source of isolate	Serology			
1	7	6	Intestinal contents	–	<1	?	Cardiorespiratory failure; postmortem myocarditis
2	8	8	Feces	RT	1	M	Acute benign pericarditis
3	9	9	Heart	8	34	M	Myocarditis, acute fever, block, fibrillation, died after 7 days, postmortem myocarditis
4	10	9	Feces, throat	RT	<1	M	Myocarditis; paroxysmal atrial tachycardia
5	11	22	Myocardium, pericardial fluid, etc.	–	1	M	Acute fulminating myocarditis; congenital gammaglobulinemia
6	12	22	Feces	RT	<1	M	Myocarditis

RT = Significantly rising antibody titer to homologous virus; Figure = titer of antibody neutralizing homologous virus; – = not done or not recorded.

diagnoses with ECHO virus type 19 These same associations of ECHO 6 infection with muscle disease and of ECHO 19 with cardiac disease emerged from an analysis of 13 400 ECHO virus infections recorded by the World Health Organization Virus Diseases Unit.[4]

It is interesting that type 6 ECHO virus was recently reported as being capable of causing Coxsackie B type disease in newborn mice We are not aware of similar reports for type 19 ECHO virus. Surprisingly ECHO virus 9 which has well-marked Coxsackie A type pathogenicity for newborn mice[6] did not show significant association with pleurodynia or cardiac disease in the analyses of the Scottish or international data though it is among the types best established as etiologically important in individual cases of cardiac disease.[9,10,20]

Table I lists the 6 cases with the best recorded evidence of an etiological association between the virus isolated and the illness. Virus was isolated from the hearts of two patients (Patients 3 and 5) and from the intestinal contents of another (Patient 1) Rising homologous antibody titers linking the infection with the disease in time were observed in 3 other patients (Patients 2 4 and 6) With the exception of Patient ? all had acute myocard tis and in 3 the illness proved fatal Five of the 6 patients were infants and where the sex was stated all were male.

Of 513 ECHO 6 infections investigated in 1967 in The Netherlands, 4 (0 8 per cent) were classified as myocarditis or pericarditis.[21] Pericarditis associated with ECHO virus 6 infection has also been described by others.[8,22] In one patient with pericarditis, serological evidence suggested infection with ECHO 9 virus. Additional evidence of the potential pathogenicity of ECHO 9 virus is provided by its recent isolation from the heart of a 16-year-old girl with acute myocarditis.[24] ECHO virus 19 was isolated from another patient but serological studies showed that this was chance carriage of this agent. Two other patients, one with myocarditis and the other with severe endocarditis, yielded ECHO 11 and ECHO 19 viruses, respectively each patient showed significant rising homologous antibody titers, but the viruses were isolated late in the illnesses and the titers suggested that the virus infections were acquired after onset of illness.[4,17] Electrocardiographic (ECG) changes have also been reported by several workers in association with ECHO virus type 6,[12] type 9 [?] and type 11 [?]

Whereas much of the proof of an etiological association in cardiac disease has of necessity depended on laboratory studies of sporadic cases, pleurodynia has frequently been reported in epidemic form and has, therefore, permitted evidence to be based on epidemiological grounds. Thus, in an outbreak of acute pleurodynia in Aden in 1967 McCracken and Wilkie[?] isolated ECHO 1 virus from 5 of 14 patients virologically investigated. During an outbreak of aseptic meningiti associated with ECHO 6 infec tion, Karzon and co-workers found that the frequency of pleurodynia was 38 per cent in adults and only 5 per cent in patients less than 20 years of age an age distribution similar to that of pleurodynia due to Coxsackie B group viruses. Kapsenberg,[21] in her 1967 study of 513 infections with ECHO 6 virus, classified 28 (5 4 per cent) as myalgia or pleurodynia. Sporadic cases of pleurodynia studied by others have been found in association with ECHO virus type 6,[?] type 8 [?] type 9 [?] and type 19 [?] Interestingly but not surprisingly the ECHO virus types associated with pleurodynia are mainly those reported in acute cardiac disease.

The ability of certain ECHO virus types to damage the cardiac or skeletal muscle of man may be linked with their ability to cause myositis in newborn mice. Others, not yet shown to infect mouselets, may be lower down the scale of human myopathogenicity and, therefore, most likely to damage the newborn or those with immunological deficiencies. Although less virulent in this respect than Coxsackie viruses, ECHO viruses are also widely prevalent and occasionally epidemic they commonly cause viremia with opportunities to reach the heart and be filtered off by myocardial cells. It seems surprising that enteroviral damage to the heart is not more frequentl

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The S_1Q_3 (McGinn White) pattern in acute cor pulmonale: A form of transient left posterior hemiblock?

I 1935 McGinn and White[1] described an electrocardiographic pattern occurring in acute cor pulmonale consisting of an S_1Q_3 configuration (as well as certain ST T changes). This pattern is usually transient but when present is highly suggestive of pulmonary embolism.

I have never been entirely satisfied with the electrophysiologic attempts to explain this S_1Q_3 pattern. The usual explanation offered is that there is clockwise rotation of the heart around its long axis related to right ventricular dilatation. The septum is supposedly oriented in such way that the initial left to right forces are projected as a Q wave on Lead III The terminal forces are directed right wardly and result in S waves in Lead I (and also in Lead V₆).

It has been emphasized subsequently that Q waves may occur in Lead V as well as in Lead III but only infrequently in Lead II, as contrasted to their occurrence in all three inferior leads in acute inferior myocardial infarction. This is supposedly related to less superiorly directed initial force in acute cor pulmonale.

Although not common finding in acute cor pulmonale, the McGinn-White pattern (S_1Q_3) when present is highly significant and usually associated with massive pulmonary embolism.

Rosenbaum[2] has recently introduced the concept of left ventricular hemiblock. A block in the anterior division of the left bundle is referred to as left anterior hemiblock (LAH) and results in left axis deviation in the frontal plane. A block in the posterior division of the left bundle is referred to as left posterior hemiblock (LPH) and results in right axis deviation (RAD) in the frontal plane with an S_1Q_3 pattern and large R waves in the inferior leads. This concept is now well founded both experimentally and clinically and has gained wide acceptance, although Watt and Pruitt[3] have advised caution in its electrocardiographic diagnosis. Curtailance

and associates[9,10] have listed some additional criteria for the diagnosis of LPH. Their criteria consist of (1) an electrical axis between +80 degrees and +115 degrees or +120 degrees, (2) terminal vector to the right (S waves in Leads I and V_6) but not necessarily anterior or with delayed conduction, (3) superiorly oriented initial vectors, and (4) clockwise rotation of the frontal plane QRS loop. They further stipulate that the following conditions have to be excluded before making a diagnosis of LPH: (1) right ventricular hypertrophy, (2) pulmonary disease, (3) extensive lateral myocardial infarction, and (4) normal vertical hearts.

Rosenbaum[3-4,7] has observed that the occurrence of LPH is much less common than LAH. He has suggested that this is because of the fact that the left posterior bundle is less likely to be traumatized because of its location in the left ventricular inflow region, because it is wider than the anterior division and also because it has a double blood supply from both the right coronary artery (posterior descending branch) as well as the left coronary artery (anterior descending branch). Other studies, however, indicate that the blood supply to the left posterior bundle is predominantly from the right coronary artery.[9]

It occurred to me that the electrocardiographic pattern in LPH may be identical (or at least very similar) to that occurring in the McGinn-White syndrome, namely, S_1Q_3 with RAD in the frontal plane. More specifically, the initial vectors are superiorly directed and the terminal vectors are inferiorly (and rightwardly) directed.[12] It would seem reasonable to conclude that (at least in some instances) the McGinn-White pattern may be due to a transient conduction defect in the left posterior bundle.

The next consideration was whether there could in some way be an impairment of blood supply to the left posterior bundle in acute cor pulmonale. If we assume that a significant, if not the major, portion of the blood supply to the left posterior bundle comes by way of the right coronary artery, then acute right ventricular dilatation might in some way interfere with adequate perfusion of the right coronary system. This could be especially true if the patient had pre-existing disease (atherosclerotic narrowing) of the right coronary artery or its posterior descending branch.

Recent studies by Fernandez and co-workers[13] and also by Maytin, Castillo, and Castellanos[1] have shown that right coronary arteriography may indeed cause RAD of the ECG (with the appearance in some cases of an S_1Q_3), presumably by transient ischemia of the left posterior bundle. On the other hand, Stein and associates[14] have found an actual increase in right coronary artery flow in acute cor pulmonale experimentally produced in pigs. It should be noted, however, that these were normal pigs and shock was not produced.

This proposal is not intended to minimize the fact that in acute cor pulmonale there may be, and in fact commonly is, marked right ventricular dilatation and actual anatomic clockwise rotation of the heart about the longitudinal axis. This is simply a postulate that in acute cor pulmonale a conduction abnormality may occur in the posterior branch of the left bundle (LPH) as an explanation for some cases that display an S_1Q_3 pattern.

Perhaps additional studies may confirm or refute my hypothesis, but at this writing it seems attractive to consider that (at least in some instances) the McGinn-White electrocardiographic pattern of S_1Q_3 occurring in acute cor pulmonale may be due to a transient LPH occurring secondary to ischemia of the left posterior bundle.

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Coronary artery surgery—Saphenous vein bypass

Surgical procedures, like drugs, are therapeutic agents. They are introduced to improve the health of man and not to *injure* him. Saphenous vein grafts for coronary arterial disease have an operative mortality *rate of* about 10 per cent, a morbidity *rate of* about 25 per cent or more (pulmonary embolism, pericarditis, pneumonia, pleuritis, hemorrhage, myocardial infarction, cardiac causalgia, and many other complications and disturbances in health), associated pain and suffering of 100 per cent, and a cost of $3,000 to $6,000 *or* more to the patient. The grafts do not cure the coronary arterial disease, about 25 per cent of the shunts close within 2 years, and the surgical procedure has never been subjected to any control studies such as sham operation or "double blind" evaluation.

Imagine any capable cardiologist prescribing a pill that had never been subjected to double-blind control studies, that might kill 1 out of 10 patients, hurt 25 per cent, produce pain and suffering in 100 per cent, cost $3,000 to $6,000 to the patient, and *never* cure him! Not only would the cardiologist not prescribe such a pill, but also the F.D.A. would *not* allow the pill to reach the *market* and the public.

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Letters to the Editor

Effect of decapitation on blood levels of creatine phosphokinase

To the Editor

In a recent paper in this JOURNAL (Wexler B C. Serum creatine phosphokinase activity following isoproterenol-induced myocardial infarction in male and female rats with and without arteriosclerosis, AMER. HEART J 79 69 19 0) the effect of isoproterenol, 500 mg per kilogram subcutaneously on the serum creatine phosphokinase (CPK) activity of Sprague-Dawley rats was reported. We wish to report that the results in that study were very likely erroneous, because of the method of blood collection employed. The author used decapitation to collect blood We have found that this produces a serious artifact as blood rushes over the cut muscles it picks up CPK from them. This leads to a blood level of CPK of approximately 60 times that present in blood from the inferior vena cava or tail vein, and 30 times that present in blood obtained by cardiac puncture. Thus, we find rat CPK activity normally to be 60 I U per liter which is only twice that in human subjects, as determined by the method of Rosalki (J Lab Clin Med 69 696 1967) whereas in the paper under discussion CPK activity was approximately 20 to 30 times that in man as determined by the same method

We found that isoproterenol, 500 mg per kilogram subcutaneously raised CPK levels 15-fold with a peak at 4 to 6 hours. The previous report placed the peak at 24 hours. Of greater importance is the fact that, with the electrophoretic technique of Van der Veen and Willebrands (Clin. Chim. Acta 13 312 1966) only the skeletal muscle isoenzyme of CPK was found in rat plasma suggesting that the cause of the increase in CPK activity was skeletal muscle necrosis secondary to isoproterenol not cardiac muscle damage In further proof of this, 100 and 250 mg per kilogram doses of isoproterenol produce as severe myocardial necrosis as the 500 mg per kilogram dose, but they produce much smaller increases in plasma CPK activity

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Reply

To the Editor

Drs. Meltzer and Guschwan state that the changes in serum CPK levels in Sprague-Dawley rats during isoproterenol-induced myocardial infarction are likely to be erroneous because the author used decapitation to collect blood. Meltzer and Guschwan indicate that as blood rushes over cut muscles it picks up CPK, which leads to greatly elevated levels of serum CPK. Because of our particular research protocol, i.e. the correlation of enzymes, lipids, steroids, etc. during the course of acute myocardial infarction, it is expedient for us to kill our animals by decapitation. We have tried several methods, but have not found that the method of killing contributes significantly to the levels of CPK which we report. Further when we decapitate our animals the relatively small mass of hyoid musculature retracts and blood spurts freely into the collecting tube with little or no contact with muscle tissue.

In my opinion, the most likely cause for the observed difference in CPK levels is due to method of measurement and "units" used to describe CPK activity In the work in question, we determined CPK activity by the fluorometric method of Willis and associates and expressed CPK activity in Sigma units, whereas Meltzer and Guschwan used the method of Rosalki and expressed CPK activity as International Units per liter measured spectrophotometrically When we use other methods and a different expression of unit our levels are very similar In fact, our values are lower than those of Meltzer and Guschwan. Therefore I believe that decapitation contributes little and methodology contributes greatly to the observed differences.

Meltzer and Guschwan also take issue with me with regard to their observed peak in CPK levels after 4 to 6 hours following isoproterenol treatment vs. my finding of a peak at 24 hours. Further they state that they find that graded doses of isoproterenol produce myocardial infarcts of equal severity and that the observed increase in CPK is due to skeletal muscle necrosis caused by isoproterenol. These findings contradict their own observations. We have had extensive experience with isoproterenol and have found that one can biologically titrate the area of myocardium infarcted with the dose of isoproterenol used. The rise in serum CPK levels is a good index of the severity of the infarct In addition to a lessened increase in CPK levels with a smaller area of myocardium infarcted, the peak increase also tends to occur at an earlier time. If Drs. Meltzer and Guschwan will re-examine my paper they will find that when animals manifest a reduced response to isoproterenol the peak increase will occur at 4 to 6 hours. We have never found any evidence of skeletal muscle necrosis at any dose of isoproterenol we have used In conclusion, I do not believe that there is such a great discrepancy between our findings and that detailed attention to methodology and unit expression would remedy the problem. I contend that my original and major assertion is correct i.e., serum CPK levels are a good *index* of early myocardial infarction.

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Uncorrected vs. corrected vectorcardiographic lead system

To the Editor:

The paper "A standard reference system for spatial vectorcardiography comparison of the equilateral tetrahedron and the Frank systems," by G. E. Burch, N. P. DePasquale, and J. A. Cronvich (AMER. HEART J. 80:638, 1970) is a contribution of considerable merit and importance. For once, data have been provided to demonstrate the clinical superiority of an uncorrected vectorcardiographic lead system over the so-called corrected. The authors' experience is in agreement with our own in several respects. First, we have always been more impressed by the similarities than the differences between loops obtained with different systems in a single patient. The emphasis in much of the available literature has always been on the differences. Second, the observation that loops recorded with the Frank system tend to be more posteriorly oriented is correct. This obscures the diagnosis of left ventricular enlargement, may lead to its over diagnosis by the unwary or may mask milder degrees of right-sided enlargement, especially in children.

Correction by electrical resistances allegedly overcomes variations in chest size, the position of the electrical center of the heart, conductivity through various tissues, and so forth. This correction smooths the contour of the loop, reduces inter individual variations caused by abnormalities, and will eliminate some of the contour irregularities now attracting the attention of a few investigators. These deviations are especially important in the geriatric age group.

Concern about lead systems continues to hinder the development and application of the vectorcardiograph as a diagnostic tool. The electrical errors that have been demonstrated in the uncorrected lead systems are also inherent in the conventional electrocardiograph. Nonetheless, accumulation of data and empirical correlations were possible with that technique and should be sought for the vectorcardiogram. Perhaps all vectorcardiographers can agree that the vectorcardiogram will provide answers not always available in the electrocardiogram when more of these correlations are made.

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Book reviews

PRINCIPLES AND TECHNIQUES OF CARDIAC PACING. By Seymour Furman M D and Doris J W Escher M D New York 1970 Harper & Row Publishers, 269 pages. Price $12.50.

Furman and Escher summarize very well the principles and techniques of cardiac pacing This subject is developing rapidly and of course, is an important new aspect of cardiology They discuss the subject thoroughly The chapters include history indications for pacing electronics, transvenous pacing permanent pacing hemodynamic changes with pacing results of pacing and other aspects The presentation is clear and the illustrations good and numerous. The authors have rendered a worthy service to all physicians, but especially to cardiologists and to those in training in cardiology Internists and cardiologists will want to purchase a copy of this book.

HARRISON'S PRINCIPLES OF INTERNAL MEDICINE, ed 6 Edited by Maxwell M Wintrobe George W Thorn, Raymond D Adams, Ivan L. Bennett, Jr Eugene Braunwald Kurt J Isselbacher and Robert G Petersdorf New York 1970 McGraw Hill Book Company Inc., 2016 pages. Price $30.50.

Harrison *Principles of internal medicine* is one of the outstand ng textbooks of med cine The approach is primarily related to the patient and the practice of med cine. The sections on the phy sician and the patient, the manifestations of disease and the pathologic physiology of disease are especially good The book is complete in that the diseases any physician is likely to encounter in a lifetime of practice are discussed very well. The colored plates are also a welcomed aspect of this book. The editors have successfully kept the medical student in mind while simultaneously providing a book for doctors as well The many contributors are experts in their respective fields. Unfortunately however in spite of an interest in producing a book of clinical medicine, some of the contributors are not in active regular practice of medicine. This is reflected in their presentations. Nevertheless, this large textbook of medicine is excellent and is highly recommended as one of the outstanding ones which can serve as a good reference book in all physicians libraries. For continuing education it should be carefully studied periodically from cover to cover by all doctors who have graduated from medical school five or more years ago.

NEW ASPECTS OF STORAGE AND RELEASE MECHANISMS OF CATECHOLAMINES. Bayer Symposium II Edited by H J Schumann and G Kroneberg. New York, 1970 Springer Verlag, 301 pages. Price $13.20

These proceedings of the Bayer Symposium II held in Grosse Ledder Germany October 9 to 12, 1969 on catecholamines are typical of many others published of symposia held within recent years. However this publication is one of the very good ones. It should interest physiologists, pharmacologists, biochemists, and physicians. The many papers are well written by outstanding participants from many countries of the world. The discussions are extremely interesting and the bibliographies are good. This book makes it possible for all interested in the subject to learn at their leisure what transpired at the meetings. The subjects discussed are most important in animal physiology especially that of man. The material presented is extensive and quite thought provoking This is an excellent publication which should have wide interest in the field of medicine. The book is worth owning.

DIAGNOSTIC ELECTROCARDIOGRAPHY AND VECTORCARDIOGRAPHY By H Harold Friedman, M.D F.A.C.P F.A.C.C. New York, 1971 McGraw Hill Book Company Inc. 486 pages. Price $13.50.

Friedman's book is intended for beginners. He introduces the concepts of depolarization and repolarization, then discusses the electrocardiograph, lead systems and other general fundamental principles of electrophysiology and electrocardiography such as nomenclature, injury currents, effects of ischemia and necrosis. This is followed by a discussion of anatomy and physiology of the conducting system, basic considerations of electrocardiography and deviation of the electrocardiogram and vectorcardiogram. The normal ECG and VCG are then defined. The initial chapters are followed by examples of the normal and abnormal ECG including arrhythmias and the common disease states. The thoughts are clearly presented and the illustrations well chosen. Since this is a relatively small book on diagnostic electrocardiography and vectorcardiography the author must and did assume that the reader had a considerable knowledge of the fundamental principles of electricity electrophysiology and cardiology The reader will find the book very useful and worth owning There are some aspects which may not be entirely correct. For example, on page 5 the author states that the indifferent electrode is at *zero* potential. It is not at zero, but is for practical purposes at *isopotential* with respect to the exploring electrodes. On pages 240 and 241 time in seconds is displayed along QRS loops of the VCG It is known that time cannot be measured accurately I conventionally recorded VCG The time interruptions of the VCG traces fuse too closely to distinguish them for counting and the isopotential region usually has a halo or there is so much fusion of the time I tervals that accurate measurement of time is not possible The VCG must be interpreted along with the ECG to measure time.

Nevertheless, this is good book to add to those already available.

Basic Factors in Bioelectric Impedance Measurements of Cardiac Output Lung Volumes and the Cerebral Circulation. Edited by Robert D Allison, Pittsburgh, 1970, Instrument Society of America, 132 pages. Price $4.00.

This publication consists of 9 papers presented at a symposium in Las Vegas, March 23-25, 1970. Almost all of the presentations and discussions were from Jan Nyboer and his associates. The principles of impedance plethysmography and some pplications of impedance measurements in biology are included. This is a good brief summary of the subject which should primarily interest physiologists nd those tudying the peripheral circulation.

Ballistocardiography and Cardiovascular Therapy. Edited by A. Falcao deFreitas, Basel, Switzerland, 1970, S. Karger AG, 357 pages. Price $18.95

This publication of the proceedings of the Second World Congress on Ballistocardiography and Cardiovascular Dynamics summarizes the discussions held during March and April, 1969. An extensive program was conducted hich included Dr I Starr the originator of ballistocardiography (BCG). Forty-nine papers were presented covering man aspects of physiologic and clinical phases of ballistocardiography. These papers summarize ery well for the reader the present concepts related to BCG. Theoretic, physical, physiologic, and clinical principles are discussed so that anyone interested in BCG will find this book useful. The format is typical of all publications of proceedings of symposia. The need or advisability of general clinical pplications of BCG by physicians is yet to be established. This is evident from study of the many papers of this book.

Atherosclerosis. Proceedings of the Second International Symposium. Edited by Richard J. Jones, New York, 1970, Springer Verlag, 706 pages. Price $18.00.

This account of the proceedings of the Second International Symposium on Atherosclerosis held in Chicago from Nov 2 to 5 1969 is quite extensive. As ith all such symposia, nothing really new is presented, but they do provide oppor tunity for discourse and review of problems. The participants presented several papers on each of the following aspects of atherosclerosis the pathogenesis, reactions of the arterial wall, thrombosis nd therosclerosis, serum lipoproteins, regulation of triglycerides, carbohydrate-lipid interactions, sterol balance and metabolism, environmental and host factors in coronary heart disease epidemiology nutritional studies, prevention and therapy drugs, nd control. This is fairly exhaustive review of the present tate of knowledge concerning therosclerosis. As has been true for t least two decades, symposia on therosclerosis have been very similar. The discussions changed very little and very little new has been presented at each succeeding one. This disease continues to kill millions of people. Nevertheless, the support for research, symposia, and various programs seems t be available if the workers engage in the studies that follow the same line of thought. Very little new of great importance has emerged. This comprehensive symposium reflects this. Regardless, this book is an effective review of the present trends in research and clinical practice. The reader ca learn of these from the book if he is not already aware of them nd can learn whether or not his own ideas are truly different from those already known or in the process of investigation. The question and answer sections are interesting as well since they point out some of the problems still confronting investigators. Atherosclerosis is one of the most serious diseases of man.

Advances in Cardiology Vol. 4 Thrombosis and Coronary Heart Disease. Edited by P. L. Halonen and A. Louhija, New York, 1970, S. Karger AG, 291 pages. Price $18.00.

This volume of *Advances in Cardiology* is concerned with advances in the understanding of thrombosis in coronary heart disease. The papers were presented t the first Paavo Nurmi Symposium held in Porvoo, Finland, September 1969. The international symposium was interest ing as reflected in the papers which included discussion of such subjects as morphology of coronary sclerosis, intramural nd intraluminal hemorrhage and coronary thrombosis, vascular endothelial damage and thrombosis and atherogenesis, physical factors in arterial sclerosis, as well as the usual discussions of platelets aggregation antithrombic gents and coronary angiography. These proceedings of the symposium are very interesting and well written. I ternists and cardiologists should find this book worth reading carefully. Coronary heart disease with myocardial ischemia is perpetual plague of man today. New ideas and symposia in this field are important in provoking thought.

Coronary Care. By Norman L. Goodland S.R.N. R.N.M.S., Bristol, 1970, John Wright & Sons, Ltd., 68 pages. Price $15.00.

This little book is written for nurses who are training for coronary care units. The presentation, therefore, is designed for beginners who have not learned the details of preclinical or clinical medicine. The principles presented are probably sufficient and accurate for beginners, but why not make them absolutely accurate even if simplified? For example, the line drawings of the electrocardiograms are so oversimplified that they are inaccurate and misleading. As simple a presentation

as a normal and wide QRS complex illustrated on page 52 contains no time lines. A normal QRS complex doubles its width when the paper speed is doubled. This is not clear from the illustration. Timing is extremely important in electrocardiography. This should be made clear even to nurses. The nurse would rarely if ever recognize atrial flutter if she expected it to look like the illustration shown on page 53. It would have been simple to trace an actual electrocardiogram if photographs of examples would be too expensive to publish. This manual should be read with caution and should be supplemented by demonstrations, lectures, and other manuals.

Books received

THE BIOCRATS. By Gerald Leach. New York, 1970, McGraw Hill Book Company, Inc. 317 pages. Price $8.95

BIOLOGICAL BASIS OF CHEMOTHERAPY OF INFECTIONS AND INFESTATIONS. By Harry Seneca, Philadelphia, 1971. F. A. Davis, 1180 pages. Price $37.50

CARDIAC REHABILITATION. By Lenore R. Zohman and Jerome S. Tobis, New York, 1970. Grune & Stratton, Inc. 248 pages. Price $12.75

FOUR HATS. By J. Willis Hurst, Chicago, 1970, Year Book Medical Publishers, Inc. 139 pages. Price $5.95

INFLUENCIAS FARMACOLOGICAS EN LA ADAPTACION CARDIOVASCULAR A LA HIPOXIA. By Mario Penna, Santiago, Chile, 1970. Universidad de Chile, 254 pages.

MODERN TREATMENT. Vol. 7 No. 3 May 1970: 1. Treatment of the systemic mycoses, by John P. Utz. 2. Treatment of calcium disorders, by Gilbert S. Gordan, New York, 1970, Harper and Row. 1500 pages per year. Price $20.00 per year

MODERN TREATMENT. Vol. 7 No. 4 July 1970: 1. Female genital infections, by David Charles. 2. Meaningful clues and physical signs in chest disease, by David E. Dines and Richard A. DeRemee, New York, 1970. Harper and Row. 1500 pages per year. Price $20.00 per year

MAYO CLINIC DIET MANUAL, ed. 4. By the Committee on Dietetics of the Mayo Clinic, Philadelphia, 1971. W. B. Saunders Company. 166 pages. Price $5.95

MEASUREMENT OF CARDIAC CHAMBER VOLUMES AND DIMENSIONS BY RADIOGRAPHIC METHODS. By Erik Carlsson, Berkeley, Calif., 1970, Department of Radiology, University of California, 24 pages. Price $3.00.

PSYCHIATRY AND THE INTERNIST. By Paul Jay Fink and Wilbur W. Oaks, New York, 1970, Grune & Stratton, Inc., 127 pages. Price $8.75

THE RESPIRATORY MUSCLES: MECHANICS AND NEURAL CONTROL, ed. 2. By E. J. M. Campbell, E. Agostoni, and J. Newsom Davis, Philadelphia, 1970, W. B. Saunders Company. 348 pages. Price $14.00

SURGICAL ANATOMY. Vols. 1 and 2, ed. 5. By Barry J. Anson and Chester B. McVay. Philadelphia, 1971. W. B. Saunders Company. 1282 pages. Price $45.00.

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Editorial

Evaluation of surgery for mitral valve disease

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Twenty years have gone by since the first commissurotomy for mitral stenosis was performed. A few years later, by extracorporeal circulation, direct approach to the mitral valve was realized. Ten years ago mitral-valve prostheses were developed which allowed total replacement in cases of advanced mitral lesions.[1,4-6,9]

We believe that the follow-up is now sufficient so that we can try to assess the results of different surgical techniques, discuss patient selection, and categorize the status of surgical therapy in view of our personal experience at Broussais Hospital.

Acquired rheumatic mitral lesions are multiple. Pure mitral stenosis with moderate scarring of the leaflets and chordae tendineae as it is observed in young women, does not involve the same surgical procedure as calcified mitral stenosis. Between these two poles, many intermediate varieties are observed in which lesions of the leaflets, chordae tendineae, and papillary muscles may reach various stages, and surgical procedure must be adapted to the type of malformation.

Indication for surgery is not limited to rheumatic inflammation. It must also be considered in congenital mitral insufficiency, ruptured chordae tendineae, bacterial endocarditis, traumatic insufficiency, and post-myocardial infarction mitral insufficiency.

First degree mitral stenosis

First degree mitral stenosis is the most frequent lesion of the mitral valve.

Pathology and clinical aspects. Closed commissurotomy for treatment of mitral stenosis can be performed most successfully in a young woman with a small heart in sinus rhythm. In our series, the operative mortality rate has been reduced to 1.5 per cent. In case of pregnancy, tolerance to mitral stenosis may sharply decrease and when response to medical treatment is unsatisfactory surgery is indicated. The operation can be performed at any time and operative risk is not increased.[11,23] Not all patients have this ideal variety with pliable valves. In many patients, associated lesions or evolutive complications will increase the operative risk and diminish long-term results.

ATRIAL FIBRILLATION. This disorder involves the risk of atrial thrombosis and systemic embolism. In atrial fibrillation patients are always prepared for operation by 6 week preoperative anticoagulant treatment. Since this technique was introduced we have never observed fresh thrombi in the left atrium or preoperative embolization. Long-term anticoagulant treatment is indicated in these patients after operation.

AORTIC INSUFFICIENCY. This condition is commonly observed with mitral stenosis. If mild aortic insufficiency can be proved

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by special diagnostic studies closed commissurotomy can still be performed The patient will benefit greatly and many years will elapse before implantation of a double prosthesis becomes necessary

TRICUSPID INSUFFICIENCY This condition must be carefully assessed before surgery Relative insufficiency related to right ventricular hypertension may be cured and disappear after commissurotomy In a case of organic tricuspid lesion in which stenosis and insufficiency are combined surgery must be performed under open heart conditions Reconstructive techniques will have great implications the use of double prosthetic valves to replace the mitral and the tricuspid valve must be reserved for patients with massive lesions of the valve [14]

CALCIFIED MITRAL STENOSIS This condition seems to be *more frequent in the male* patient In a young patient with pure mitral stenosis without any insufficiency closed commissurotomy should be tried Commissurotomy will certainly not be perfect but we have observed many long term and gratifying results Of course if calcification involves both the mitral ring *and leaflets the mitral apparatus must be resected and a prosthesis inserted*

ASSOCIATED PULMONARY HYPERTENSION This condition is frequently observed after a long pathologic evolution Closed commissurotomy *may obtain very encouraging* results in this variety of mitral stenosis barring the cases of long duration in which pulmonary resistance is very high and fixed

MITRAL STENOSIS AND INTERATRIAL SEPTAL DEFECT Surgery must be performed under open heart conditions Commissurotomy can be performed through the atrial septal defect Whenever a conservative operation seems feasible closure of the atrial septal defect requires *a perfect function of the* mitral valve [24-26,28]

Surgical techniques We still prefer the left transatrial approach which we use routinely seldom do we use the right-sided or transventricular approaches

The transatrial approach is easy to perform fast and safe Since 1952 we have devised a mechanical dilator and opening both blades usually splits both commissures in 70 per cent of patients, one in 30 per cent of patients and usually the *anterolateral commissure* [11,14,17,27]

In a series of 3 000 closed mitral commissurotomies we observed very few traumatic mitral insufficiencies related to a too energetic and unreasonable use of the dilator *It is important to stress that opening* the dilator splits the commissures with its first proper introduction Commissural opening is then total or partial if only partial it is of no use to try to ameliorate this mitral result by multiple introductions of the dilator This could be dangerous for the valves or the mitral annulus.

In complicated or evoluted cases the operative mortality rate is certainly higher (6 per cent) than in the uncomplicated case of mitral stenosis in the young female patient

Follow-up In regard to long term follow up nobody dares to discuss the palliative nature of mitral commissurotomy today Even in the most favorable cases such as mitral stenosis in the young female patient long term follow up shows recurrence of symptoms around the tenth year Indeed some patients will maintain good postoperative results *after 12 or 15 years* but *they constitute a minority (7 per cent)* Also in some patients (30 per cent) restenosis will appear within 5 years following surgery restenosis having no relation to the anatomical results of the first operation and in spite of long term antibiotic and anticoagulant therapy

This argument among *others seems* to support the use of blind commissurotomy in pure mitral stenosis as opposed to open-heart commissurotomy Surgical series show a higher operative mortality rate for the open heart approach which we believe incongruous with the gravity of the treated lesion Besides it may lead to an over *estimation of damage to the mitral* valve and result in implantation of a prosthesis.[25]

RESTENOSIS Restenosis of the mitral valve brings up some problems and several factors must be considered the age of the patient associated valvular lesions and the lesion observed during the first operation [37,43]

In a young female patient we resolutely choose a conservative approach we perform a second blind commissurotomy If

fluoroscopic examination did not show any mitral calcification and if absence of regurgitation has been proven by left ventriculography.

In an older patient with calcified valves and the suspicion of atrial thrombosis, surgery is performed under open-heart conditions. In such case, a conservative procedure is often impossible and more often the mitral valve has to be resected and replaced by a prosthesis. Our final surgical series includes a small number of patients, on whom we performed a third blind commissurotomy with success.

Second degree mitral valve disease

Combined mitral lesion is in a completely opposite pole from mitral stenosis. Mitral anatomy is deeply altered by combined stenosis and insufficiency by valvular and annular calcifications by shortening of the chordae tendineae and by thickening of the papillary muscles. In such a case the only choice is implantation of a mitral prosthesis. Operative risk is then quite different in this type of mitral valve disease many other lesions are associated. Damage to the lungs, kidney liver and myocardium are frequently observed and the postoperative course is affected by these associations.

During operation complications may occur related to decalcification of the annulus near the mural leaflet, the existence of massive atrial thrombosis or the risk of air embolism. This last risk is quite dangerous in open-heart mitral surgery chiefly with the right-sided approach.[1]

Routine use of median vertical sternotomy with scrupulous respect to the strict rules of aortic venting has allowed us to reduce this risk greatly without however suppressing it totally.[21]

As far as the choice of prosthesis is concerned we resolutely adopt the Starr valve with a Silastic ball. We have used the disc valve in a few patients with small ventricular cavities which would not admit a cumbersome cage.[illegible]

We do not think that the Starr valve is the ideal prosthesis but we think it is less dangerous than other types. But we are in complete disagreement with every year's proclamations praising new methods of valve replacement while last year's techniques had already been presented as ideal. Only long and complete research in the experimental laboratory will help to prepare the ideal prosthesis whose hemodynamic qualities if necessary are not sufficient.

Our operative mortality rate is high. Our series includes all operated patients without exception (desperately ill patients, emergency cases, reoperations for prosthesis thrombosis, etc.) 20 per cent in 500 mitral prostheses 30 per cent in 250 double valvular replacements 40 per cent in 80 triple valvular replacements.

Most of the patients we operate on are Class IV patients (New York Heart Association classification). The most frequent fatal complications are low cardiac *output*, cerebral complications, and renal or hepatic failure. The risk of early thrombosis during *hospitalization* in our surgical service can be figured around 5 per cent with any type of prosthesis. This type of complication is very hard to control. It is mainly observed in patients with aneurysmal dilatation of the left atrium or postoperative arrhythmia when a low cardiac output appears.[11,14,38]

In spite of very stringent long term anticoagulant therapy thromboembolic complications are still observed in long term *follow-up* (0 per cent). This complication is the main source of late death with leakage by partial disinsertion of the prosthesis, bacterial endocarditis, cardiac insufficiency.[illegible]

Our first patient with a mitral Starr prosthesis was operated on in 1962 and died 8 years later. On postmortem examination a fibrinocruoric cylinder was found around the cage in the left ventricle and the ball was completely blocked at the end.

Third degree mitral valve disease

Mitral insufficiency has many origins. In adults, in 20 per cent of our cases mitral insufficiency is related *to dilatation of the* annulus with minimal alterations of valve tissue and chordae tendineae. We originally used reconstructive techniques for this type of lesion mainly the posteromedial annuloplasty or modifications of this, as described by Kay[illegible] Merendino[illegible]

or Wooler[49] and their associates But like many authors, we observed a high rate of recurrence of mitral insufficiency and decided that our patients with this lesion should undergo mitral valve replacement.[3,34]

In 1967 Carpentier and co workers[9,10] proposed to correct mitral insufficiency by remodeling the mitral annulus on a metallic ring suitably shaped and sized In this technique the prosthetic ring is sutured to the mitral annulus so that the normal orifice area is preserved and the plicatures are concentrated on multiple points at the mural leaflet and at the commissures This avoids the narrowing of the mitral area and prevents the subsequent dilatation of the mitral annulus a common cause of recurrent insufficiency after surgery This technique was used very cautiously at the beginning but as the number of cases with successful results has increased it has been selected in all cases of insufficiency with dilatation of the annulus without alterations of valve tissue or chordae tendineae lesions. In 3 years it was used on 50 patients, with a mortality rate of 10 per cent and excellent long term results Follow up is still too limited to assess these results, but this conservative technique avoids anticoagulant therapy it allows pregnancy in young women and allows a pilot to fly a plane. This technique is also currently used in patients from foreign countries where anticoagulant therapy is difficult or impossible with any security It is also worthwhile to note that a metallic ring can also be used in the tricuspid position to control tricuspid insufficiency by dilatation of the annulus. But in the great majority of cases, a conservative technique is impossible because of alterations in the valve tissue and chordae tendineae

In most cases we use the Starr valve with a Silastic ball (we had some unhappy experience with the metallic ball first model and we never used the last type)

The risks of anticoagulant therapy in patients unable for any reason to tolerate it led us to the use of heterografts. Experimental investigations have shown the satisfying hemodynamic function of frame-mounted heterografts implanted in the mitral area.[5,7] Clinical experience was limited to a short series of patients. It must be said that results in the first series were discouraging Graft failures were observed in almost 50 per cent of patients within the first 2 years and appeared to be closely correlated to the method of preservation of the graft (mercurial salts, formalin) Carpentier and associates[8] developed a suitable method of preservation making possible the decrease of antigenicity of heterologous tissues and the prevention of long term denaturation of collagen. This method has shown considerable promise. Of 17 patients with mitral valve replacements being followed up for at least two years no failures have been observed up to now However we still consider this method to be under clinical evaluation and indications for heterograft valve replacement must be limited to selected patients in whom anticoagulant therapy cannot be used

In some very rare cases following subacute bacterial endocarditis, a tear in the valve or ruptured chordae tendineae are observed A tear in the valve can be repaired by a Teflon patch of appropriate size. In ruptured chordae tendineae, plication of the ruptured leaflet is usually performed with good results, combined with posteromedial annuloplasty or Carpentier's annuloplasty in most cases it is possible to avoid use of a prosthesis. We do not have great experience with mitral insufficiency resulting from papillary muscle dysfunction that occurs on the basis of atrophy and scarring of the papillary muscle after healing of a myocardial infarct and which more commonly involves the posterior papillary muscle In three such cases a Starr prosthesis was implanted with success.[13,31,32]

Finally we have observed three patients with congenital mitral insufficiency with a parachute type of valve Any conservative technique was impossible and in these three children (4 5 and 6 years old) prostheses had to be used

Conclusions

Surgery for mitral valve disease has reached the advanced stage of development and the surgeon is able to face the various anatomical varieties with efficient tech

niques, the best one being blind commissurotomy for mitral stenosis. Implantation of a mitral prosthesis involves a much higher operative mortality rate it is a risk to be taken only after scrupulous analysis. However operative mortality has been reduced by several factors improvement of postoperative care, routine respiratory assistance, control of cardiac arrhythmias, treatment of low cardiac output, early anticoagulant therapy But secondary complications are still frequent in patients with a prosthesis the bondage of permanent anticoagulant therapy remains very heavy Implantation of a valvular prosthesis cannot be considered as a routine procedure for all mitral lesions.

The perfect prosthesis is not yet available and this notion is important in operative selection blind commissurotomy in the young patient is easily decided when indicated it is not as easy to decide when an open operation is necessary with the risk of valve replacement, as it is well known how long some mitral lesions can be tolerated and well compensated

Beside the technical problems the human environment must be considered. It is necessary to discuss with the patient all the consequences of implantation of an artificial prosthesis, chiefly in a young woman.

Valve replacement cannot be considered as a routine procedure. Only when medical treatment has failed in improving the patient will valve replacement be undertaken

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Left ventricular aneurysm: Analysis of electrocardiographic features and postresection changes

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The clinical, electrocardiographic, radiographic, and hemodynamic features of left ventricular aneurysm have been extensively studied over the last 15 years.

Since 1958, numerous series of successful resection have been presented in which the clinical, radiographic, and hemodynamic results of aneurysmectomy have been reviewed. However, no detailed study of the electrocardiogram (ECG) before and after surgery has been attempted. This is the subject of the present paper.

Material and methods

Patients operated upon at St. Luke's Episcopal Hospital between January, 1958, and March, 1969, were included in this study. The great majority of these patients were presented in a recent publication.

Pre- and postoperative 12 lead ECG's were studied; the postoperative tracings were usually recorded a few days after surgery, before the patients left the hospital. Satisfactory tracings were obtained in 26 cases. In these patients age and sex were recorded. The interval between myocardial infarction and surgery, whenever definite, was noted. In some, no previous myocardial infarction could be recalled and others had had multiple attacks.

The size of the aneurysm was assessed by measurement of the resected specimens sent for pathologic examination after surgery. This approach cannot evaluate the dynamic aspects of the aneurysm, but for a retrospective study it was considered more accurate than x-ray evaluation or direct surgical estimate.

The QRS voltage and S-T-segment elevation were compared in the pre- and postoperative ECG. These features were correlated with the size and "age" of the aneurysm. The ECG changes seen in different leads of a 12 lead ECG were used to localize the "electrical position" of the aneurysms. Since there exists no absolute criteria for the ECG diagnosis of ventricular aneurysm, changes consistent with transmural infarction with or without persistent S-T elevation were used for ECG localization of the aneurysmal site.

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Table I Pertinent data of cases with left ventricular aneurysm

No	Patient	Age (years)	Sex	Age of aneurysm (months)	Size (sq cm)	Location	QRS duration (sec)	
							Preoperative	Postoperative
1	T I	47	M	7	80	Anterior	0 08	[illegible]
2	A R.	61	M	192	108	Anterior	0 12	[illegible]
3	M J	60	M	7	70	Apical	0 11	[illegible]
4	O J	73	M	3	48	Anterior	0 11	[illegible]
5	S. J	52	M	48	20	Inferior	0 10	[illegible]
6	B R.	56	M	2	28	Anteroseptal	0 08	[illegible]
7	A. B	58	M	17	35	Apical	0 09	[illegible]
8	C. L.	38	M	5	21	Anterior	0 09	[illegible]
9	F A	66	F	?	?	Anterior	0 08	[illegible]
10	K. R.	43	M	144	12	Anterolateral	0 15	0 11
11	H N	68	M	10	44	Anteroseptal	0 11	0 11
12	B W	54	M	24	88	Anterior	0 12	[illegible]
13	J P	67	F	36	35	Antero-inferior	0 08	[illegible]
14	S. L.	59	M	33	67	Anterolateral	0 12	[illegible]
15	C. O	53	M	3	51	Anterior	0 08	[illegible]
16	T L.	57	M	2	55	Anterolateral	0 12	0 11
17	J A.	62	M	144	22	Anterior	0 11	[illegible]
18	H J	64	M	11	32	Anterior	0 08	[illegible]
19	W M	46	M	14	?	Anteroseptal	0 09	[illegible]
20	R. H	60	F	9	95	Anterior	0 12	0 11
21	M G	41	M	2	45	Anterior	0 09	[illegible]
22	K. E.	45	M	4	50	Anterior	0 06	[illegible]
23	K. J	62	M	30	30	Anterior	0 10	[illegible]
24	C. R.	68	M	7	55	Lateral	0 11	0 11
25	A T	72	M	3	77	Anterior	0 08	[illegible]
26	L. L.	65	M	2	275	Anterior	0 10	[illegible]
Mean		60		35 8	51		0 0992	[illegible]
Median		59		9	50			
			Men 88 4 % Women 11 6			Anterior 21 Inferior: 1 Apical 2 Lateral 1 Antero-inferior: 1		

The criteria set by Lamb[4] and by Massie and Walsh[5] were used for the definition of abnormal Q waves and also for localization of infarction as anterior anteroseptal anterolateral and inferolateral ECG changes consistent with transmural infarction with or without persistent S-T elevation were used for indirect localization of the aneurysmal site The QRS axis was calculated by plotting the net QRS area in the triaxial system [5]

Results

Patient age Ages ranged from 38 to 73 years the average being 60 and the median 59 years (Table I)

Sex There were 23 men (88 4 per cent) and 3 women (11 6 per cent) in the study (Table I)

Interval between myocardial infarction and operation (*age of the aneurysm*) This interval could be documented in 24 patients and ranged from 2 months to 16 years. The mean time interval was 35 8 months and the median 9 months (Table I) This difference in mean and median time was the result of 3 patients with more than 12 years between the time of infarction and operation together with 14 patients with less than 1 year between these events.

Size. The tissue specimen could be accurately measured in 24 [illegible] two

QRS axis (degrees)		S-T deviation (mm)		Net R wave (mm.)		Q-wave incidence (I all leads)	
Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative
120 (RAD)	+120 (RAD)	5	0	−4	−4	5	5
60 (LAD)	− 60 (LAD)	0	0	4	4	3	3
32 (NAD)	+ 32 (NAD)	5	3	5	2	0	0
70 (LAD)	− 70 (LAD)	2 5	2 5	0	0	5	3
50 (NAD)	+ 35 (NAD)	0	0	0 5	2 8	1	1
20 (RAD)	+ 90 (NAD)	3	1	−2	0	0	0
40 (LAD)	− 40 (LAD)	1	0	3	4	4	0
20 (LAD)	− 30 (LAD)	4	2	2	4 5	5	3
30 (LAD)	− 15 (LAD)	2 5	2 5	4	6	5	4
65 (LAD)	− 65 (LAD)	3	0	4	4	3	1
0 (NAD)	0 (NAD)	3 5	2	2 5	4 5	5	0
120 (LAD)	− 40 (LAD)	5	0	0	3 5	0	0
70 (LAD)	− 10 (LAD)	7	2	4	6 5	6	0
120 (RAD)	+ 30 (NAD)	2 5	0	−3	4	5	5
65 (NAD)	− 30 (LAD)	2 5	0	1 5	4	5	2
60 (NAD)	+ 60 (NAD)	1	0 5	2	9	4	2
60 (LAD)	− 45 (LAD)	2	1	4	5 5	2	1
150 (RAD)	+ 40 (NAD)	4	2 5	3	9	6	4
25 (LAD)	− 25 (LAD)	0	0	6	9	3	3
60 (LAD)	− 60 (LAD)	3 5	4	2 5	4	5	5
120 (RAD)	+ 45 (NAD)	3	2	−5	0	5	4
62 (NAD)	+ 60 (NAD)	3 5	0	1	2	4	5
45 (NAD)	+ 45 (NAD)	0	0	4	4	4	4
30 (LAD)	− 50 (LAD)	2	1	1	4	1	1
150 (RAD)	+150 (RAD)	2 5	2	−1	4	6	3
120 (LAD)	− 80 (LAD)	1	1	−1	1	1	0
		3 04	1 31	1 46	3 74	4 04	2 68

AD- 13 points LAD- 14 points
AD: 7 points NAD: 10 points
AD 6 points RAD 2 points

multiple segments were sent. The excised area ranged from 20 to 108 sq cm. The average size was 51 sq cm the median was 50 sq cm A regression analysis of size versus age of aneurysm was made but there was no significant correlation between these two parameters (correlation coefficient, 0.0275 number of patients, 24)

Electrocardiographic localization In no patient was there a discrepancy between the exact anatomic localization as determined at the time of operation and that suspected by the ECG changes. The aneurysms were anterior anteroseptal or anterolateral in 21 cases which were classified together as "anterior" There was 1 strictly lateral, 1 inferior 1 anteroinferior and 2 inferolateral lesions (Table I)

Rhythm. All patients had sinus rhythm

QRS axis This ranged from −70° left to +150° right. Thirteen patients had left axis deviation (LAD) specified as less than 0° 6 had right axis deviation (RAD) specified as greater than 90° and 7 had an axis within normal limits (NAD) i.e. between 0° and 90° There was no statistical correlation between aneurysm size and axis deviation (r value 0.004) The average "age" of the aneurysm in patients with LAD was greater (49 7 months) than that of patients with right (9.5 months) or normal (15 1 months) axis. However the

variation within this group was so large that these differences could not be stated to be different on a statistical basis The median test had to be used because the variances within groups were not homogeneous ($\chi^2 = 1\ 106$)

QRS duration The mean duration (26 patients) was 0 10 second This was plotted against aneurysm size and age There was a weak correlation with the aneurysm size which did not attain statistical importance (correlation coefficient 0 1298 24 patients) QRS duration increased with the age of the aneurysm and this correlation was significant at the 99 per cent confidence level (correlation 0 594 24 points)

R wave net positivity This was calculated in Lead I in anterior and lateral lesions and in a aVF in the inferior and inferolateral lesions. There was a weak inverse relationship between R wave net positivity aneurysm size not attaining statistical significance (correlation coefficient 0 1391 24 points)

Abnormal Q-wave surface distribution Twenty-one patients had abnormal Q waves in 90 of the 252 cumulative standard limb or precordial leads. The patients with larger aneurysms had wider distribution of Q waves in the ECG The number of leads in the 12 lead ECG in which abnormal Q waves were found correlated with aneurysm at the 95 per cent confidence level (correlation coefficient 0 443 20 points)

S T–segment elevation Twenty two patients had S-T segment elevation above the baseline in one or more of the 12 ECG leads The greatest elevation found in any lead of each individual tracing was selected and its correlations were found Of the 4 patients having no S-T–segment elevation 3 had an anterior and 1 an inferior aneurysm

Postaneurysmectomy changes

QRS axis In thirteen subjects with LAD there was a change in direction from $-59\ 23°$ to $-43\ 45°$ This was not statistically significant Actually in no patient did LAD disappear post-operatively although it became less leftward in 4 subjects Similarly the change was not statistically significant in subjects with NAD (from 38 42° to 28 85°) In patients with RAD there was a significant change at the 95 per cent confidence level (from 130° to 79 16°) Actually only 2 patients retained RAD after aneurysmectomy (Fig 1)

QRS duration This decreased from a preoperative average of 0 09 second to a postoperative of 0 08 second This change was significant at the 99 per cent confidence level (t value 3 238)

R wave net positivity This increased from an average value of 1 36 mm to a postoperative average of 3 74 mm This change was significant at the 99 per cent confidence level (t value 5 013 Figs 1 and 2)

Abnormal Q wave surface distribution. The number of leads with abnormal Q waves decreased from a preoperative 4 04 to a postoperative 2 68 average This change was significant at the 99 per cent confidence level (t value 3 690) In 3 out of 21 patients the abnormal Q waves completely disappeared from all leads (Fig 2)

S T–segment elevation The S-T segment elevation measured in the lead with maximal deflection decreased from a preoperative average of 3 04 mm to a 1 31 mm average post-operatively This was significant at the 99 per cent confidence level (t value 4 77) In 7 of 22 patients the S-T elevation completely disappeared (Fig 2)

Discussion

The sex distribution in our experience agrees with the majority of published studies[6,7] Only Johnston Lam and Wright[4] found a greater incidence among women

The ECG changes consistent with anterior localization predominated an observation previously reported in necropsy studies[7,9] The localization of the aneurysm estimated by the ECG was confirmed in every case at operation

In our series aneurysm size was not proportional to the interval between myocardial infarction and aneurysmectomy (age of the aneurysm) a finding in agreement with previous studies.[10]

Most authors have pointed out that there is a significant axis deviation either to the right[11] or to the left[12-16] in patients with ventricular aneurysm Goldberger and Schwartz[17] have stressed that the left axis deviation and marked rotation of the heart

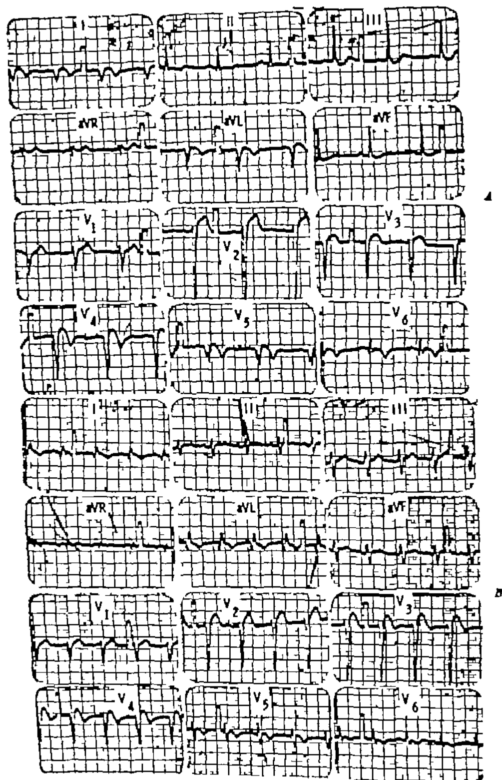


Fig. 1 Marked increase in R-wave positivity in Leads I and V_L, together with change from right axis deviation, 9 days post-operatively A Preoperative B Postoperative.

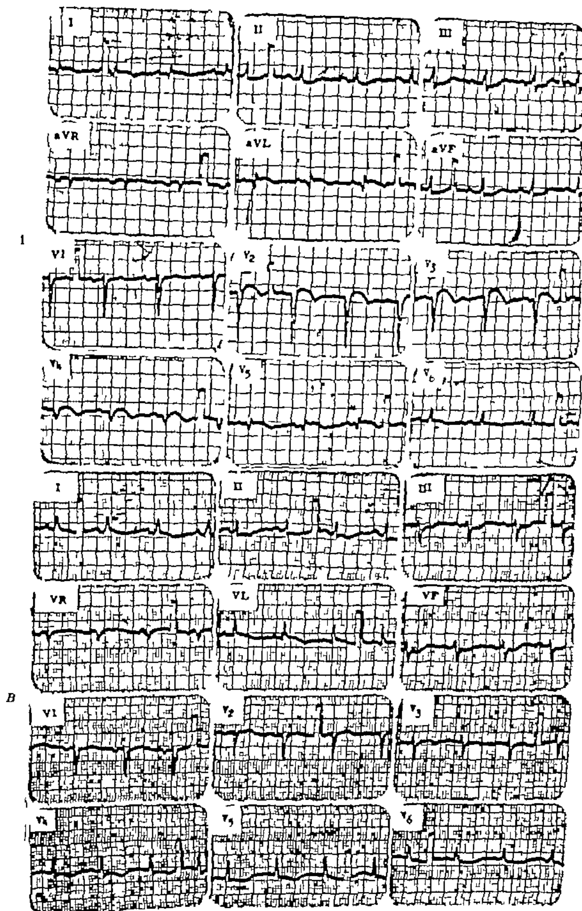


Fig. 1 Disappearance of abnormal Q-wave changes and S-T elevation 4 days after aneurysmectomy. *A* Preoperative; *B* Postoperative.

are associated with a positive R wave in aVR which is frequently found in cases of left ventricular aneurysm Soulié Laham and Papanicolis[14] demonstrated that in very large aneurysms or in those developing shortly after infarction of a normal-sized heart a right axis deviation is seen. On the contrary left axis deviation is associated with small aneurysms or with those slowly evolving in hearts already enlarged or hypertrophied Moreover left axis deviation was found more often in anterior infarctions. Others[1] have noted that left axis deviation is more frequent with larger sized aneurysms, however statistical analyses were not done in these studies. We did not attempt any correlation between aneurysmal site and axis, because our series was too heavily representative of anterior aneurysms. We did not find any correlation between axis and size. Our only positive finding was a weak correlation between age of the aneurysm and left axis deviation which could not be said to reach statistical significance. Similar findings were recorded by Soulié, Laham, and Papanicolis and by Gurman who found that the mean QRS axis moves leftward with time

It is difficult to explain the postoperative changes as regards QRS axis. In no case did a left axis of the QRS change to normal or right axis, while in most cases with right axis deviation, the QRS axis returned to normal post-operatively

We think that most of our patients with LAD had a left anterior hemiblock[18] The anterior division of the left bundle is closely associated to the outflow tract of the left ventricle and is perfused only by the anterior descending coronary artery It is thus very vulnerable to hemodynamic stress (aortic stenosis) and to any ischemic or fibrotic lesion of the anterior portion of the left ventricle.[n] The axis deviation would not be expected to change after aneurysmectomy since the lesion of the left anterior division would still exist.

All of our patients with RAD also had anterior aneurysms. The posterior division of the left bundle runs along the left ventricular inflow tract which is not subjected to significant hemodynamic stress. It terminates at the posterior papillary muscle, and has a dual vascular supply from both the anterior and posterior descending coronary arteries. This branch is thus relatively well protected from mechanical or ischemic injury

Our patients with RAD did not present the ECG criteria of left posterior hemiblock.[n] A more likely explanation of the axis deviation is an extensive loss of left ventricular potential which causes a deviation of the heart vector to the right, since it is unopposed by left-sided forces[n,n] (Fig 1) With aneurysmectomy the ECG left ventricular window of necrosis was excised and replaced by normal muscular tissue. This change should produce a more normal axis.

Many authors have commented upon the loss of R wave in standard leads when an aneurysm appears.[n,n] This was evident in our series. The loss of R wave deflection however did not strongly correlate with the size of the aneurysm

Ventricular aneurysm has been noted to be associated with wide distribution of abnormal Q waves in the standard ECG Previous authors[n] have not found a correlation between the number of leads with abnormal Q waves and the size of the aneurysm They concluded that the surface distribution of Q waves represents the extent of the transmural infarction which does not parallel the external bulging of the aneurysmal wall[n] In our statistical evaluation however a significant correlation was found between the number of leads in which abnormal Q waves were present and the aneurysm size. Following the surgical removal of the infarcted area the surface distribution of abnormal Q waves strikingly decreased and in some instances all abnormal Q waves disappeared Concomitantly there was a spectacular increase in net R-wave positivity after aneurysmectomy In some cases R waves appeared where there was only a QS wave preoperatively as if the necrotic tissue had been eradicated, permitting the potential of normal muscle to become evident.

Persistent S-T-segment elevation following myocardial infarction has been regarded as ECG evidence of ventricular aneurysm. In a group of patients studied

6 months or more after infarction Cronin and James[24] found no more aneurysms in those patients with elevated S-T segments than in those with isoelectric S-T segments In estimating the significance of S-T–segment elevation the location of the aneurysm appears important since in three series[7,13,27] S-T segment elevation was found in 79 to 100 per cent of anterior aneurysms but in only 50 per cent of those located inferiorly Of our patients with no S-T–segment elevation 3 had an anterior and 1 an inferior aneurysm The number of patients with inferior myocardial aneurysms were too few in our series to permit any conclusion

It should be mentioned that since our postoperative studies were obtained a few days after surgery some of the findings could be attributed to the results of thoracotomy and surgical manipulation However in 5 patients in whom follow up tracings were obtained approximately 1 year post-operatively no significant changes from the predischarge ECG s were found

Summary and conclusions

From statistical analysis of the ECG s of 26 patients recorded before and after aneurysmectomy we think that the following data emerge

1 Aneurysms are more frequent in men Anterior locations predominate Older aneurysms are not larger

2 The ECG axis, loss of R wave positivity or degree of S-T–segment elevation cannot predict the size of the aneurysm In contrast increased QRS duration and body surface distribution of abnormal Q waves suggestive of myocardial necrosis correspond to larger aneurysms

3 After aneurysmectomy R wave positivity increases and abnormal Q waves and S-T–segment elevation diminish and may even disappear

4 In contrast to right axis deviation which diminishes and may even disappear after aneurysmectomy left axis does not change significantly This different behavior may be due to the different etiology of these axis deviations. Right deviation is probably caused by loss of left sided potentials while left axis deviation is frequently produced by left anterior hemiblock

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6 months or more after infarction Croden and James[24] found no more aneurysms in those patients with elevated S-T segments than in those with isoelectric S-T segments. In estimating the significance of S-T–segment elevation, the location of the aneurysm appears important, since in three series[7, 12, 27] S-T segment elevation was found in 79 to 100 per cent of anterior aneurysms but in only 50 per cent of those located inferiorly. Of our patients with no S-T–segment elevation, 3 had an anterior and 1 an inferior aneurysm. The number of patients with inferior myocardial aneurysms were too few in our series to permit any conclusion.

It should be mentioned that since our postoperative studies were obtained a few days after surgery, some of the findings could be attributed to the results of thoracotomy and surgical manipulation. However, in 5 patients in whom follow-up tracings were obtained approximately 1 year post-operatively, no significant changes from the predischarge ECG's were found.

Summary and conclusions

From statistical analysis of the ECG's of 26 patients recorded before and after aneurysmectomy, we think that the following data emerge:

1. Aneurysms are more frequent in men. Anterior locations predominate. Older aneurysms are not larger.

2. The ECG axis, loss of R wave positivity, or degree of S-T–segment elevation cannot predict the size of the aneurysm. In contrast, increased QRS duration and body surface distribution of abnormal Q waves suggestive of myocardial necrosis correspond to larger aneurysms.

3. After aneurysmectomy R wave positivity increases and abnormal Q waves and S-T–segment elevation diminish and may even disappear.

4. In contrast to right axis deviation which diminishes and may even disappear after aneurysmectomy, left axis does not change significantly. This different behavior may be due to the different etiology of these axis deviations. Right deviation is probably caused by loss of left-sided potentials, while left axis deviation is frequently produced by left anterior hemiblock.

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Table I Patients with pericardial windows Histology of pericardial biopsy

Final diagnosis	*N*	*Acute and chronic inflammation*	*Normal*	*Fibrinous*	*Noncaseating granuloma*	*Fibrosarcoma*
Purulent pericarditis	5	5				
Congestive heart failure	4	2	2			
Chronic idiopathic effusion	4	3	1			
Acute myocarditis	1	1				
Acute benign pericarditis	1	1				
Postpericardiotomy syndrome	1	1				
Tuberculous pericarditis	1				1	
Fibrosarcoma	1					1
Histoplasmosis	1			1		
Uremic pericarditis	1			1		
Totals	20	13	3	2	1	1

chronic or recurrent tamponade, and (3) to biopsy the pericardium in an attempt to establish the etiology of an effusion.

Pericardiocentesis was done on 21 patients, twelve male and nine female, by means of the subxiphoid or apical approach utilizing electrocardiographic monitoring. Pericardiocentesis was performed (1) to relieve tamponade and (2) to obtain pericardial fluid to establish the etiology of the effusion, especially in suspected purulent pericarditis.

The hospital records were examined for pre and postbiopsy diagnoses and evidence of postoperative complications. A diagnosis of surgical wound infection was made if purulent drainage was associated with fever, leukocytosis, and the recovery of pathogenic organisms on culture of the drainage.

Results

Pericardial windows. The 20 patients who had pericardial windows ranged in age from 1 to 73 years with a mean age of 39 years.

The final diagnoses are listed in Table I. Purulent pericarditis, the most common etiology of effusion, occurred in five patients (25 per cent). Congestive heart failure was the etiology in four patients (20 per cent) and chronic idiopathic effusion in four patients (20 per cent). The histologic diagnoses from the pericardial biopsies were frequently not helpful in establishing an etiological diagnosis, 13 patients (65 per cent) showing either acute or chronic inflammation (Table I). In one patient *Histoplasma capsulatum* was cultured from the pericardial fluid, but the pericardial biopsy showed only fibrinous pericarditis.

Thirteen of the 20 patients had at least one complication in the postoperative period (Table II), the most common was secondary wound infection in eight patients (40 per cent). Seven patients (35 per cent) developed atelectasis with pleural effusion, four patients (20 per cent) developed chronic sinus tracts, two patients (10 per cent) developed pneumonia with respiratory failure requiring endotracheal intubation, and one patient (5 per cent) developed atrial flutter during the operative procedure. There were three deaths but in only one case was there a possible association between the biopsy procedure and the patient's death. A 73-year-old woman with hypertensive cardiovascular disease and chronic congestive heart failure had a diagnostic pericardial window for chronic pericardial effusion and possible tamponade. Three days after performance of the pericardial window she developed a bleeding gastric ulcer which was treated by oversewing of the ulcer and vagotomy. Four days later she had another gastrointestinal hemorrhage from multiple shallow mucosal ulcerations, necessitating a partial gastrectomy and Billroth II procedure. Shortly after her third surgical procedure she developed a wound evisceration and respiratory failure; she then died.

The other two deaths were unrelated to

Pericardial windows or pericardiocentesis for pericardial effusions

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The optimal approach to the diagnosis and therapy of pericardial effusion has been debated in the medical and surgical literature since the first pericardial tap was reported from Vienna in 1841 [1] Pericardial biopsy and drainage have been used as a diagnostic and therapeutic procedure for patients with pericardial effusions [2,3] However procedures such as pericardiectomy and pleuropericardial windows necessitate thoracotomy and general anesthesia In addition pleural pericardial windows may rapidly close due to adhesions, necessitating further drainage procedures. In recent years a percutaneous pericardial window has been advocated by Weinberg and associates[4] as a simple method of obtaining a pericardial biopsy and drainage of pericardial effusion

Since there has been no recent comparison of the morbidity or mortality rates with percutaneous pericardial windows compared with pericardiocentesis a retrospective analysis of the records of patients who underwent these procedures was performed to define the indications for and the complications of pericardiocentesis and pericardial windows.

Material and methods

The hospital records of patients admitted to Parkland Memorial Hospital in Dallas in whom percutaneous pericardial windows and/or pericardiocenteses were performed during the years 1966 to 1969 were reviewed Twenty patients, eleven male and nine female, had percutaneous pericardial windows performed by means of the method described by Weinberg and colleagues.[4] Briefly the procedure consisted of entering the pericardium by splitting the fourth and fifth left costal cartilage and remaining extrapleural this was often accomplished with the use of local anesthesia Penrose drains were left in place to permit continuous percutaneous drainage of the pericardial fluid for 24 to 72 hours. In each procedure a biopsy of the pericardium was taken for pathological examination and culture Pericardial windows were performed (1) to provide drainage of a purulent pericardial effusion (2) to relieve

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Table IV. Pericardiocentesis. Final clinical diagnosis

	No. of patients	Diagnosis from pericardiocentesis
Uremic pericarditis	3	
Congestive heart failure	3	
Acute benign pericarditis	3	
Postpericardiotomy syndrome	2	
Stab wound of chest	2	
Purulent pericarditis	2	2
Dissecting aneurysm	1	
Scleroderma	1	
Histoplasmosis	1	1
Tuberculosis	1	1
Acute myocarditis	1	
Chronic idiopathic effusion	1	
Total	21	

cardial window. In four of the ten patients the window was performed for relief of recurrent tamponade and in four of the ten the procedure was done to drain a purulent effusion. There were four diagnostic pericardial biopsies which had been preceded by a tap. In two of these, a diagnosis that was missed initially by the pericardiocentesis was made from the biopsy (tuberculous pericarditis and acute myocarditis).

Discussion

Proudfit and Effler[4] in 1956 reported upon 16 pericardial biopsies through a pleuropericardial window and found a specific etiologic agent in five of the 16. Complications and morbidity of the procedure were not specifically dealt with by saying "Postoperative reactions were mild." Williams and Soutter[5] performed open pericardial and myocardial biopsies on 42 patients who had unequivocal pericardial or myocardial disease of uncertain etiology. They concluded that the indications for pericardial biopsy should be (1) chronic or recurrent pericarditis of uncertain etiology, (2) unexplained hemopericardium, and (3) possible constrictive pericarditis. The problem of secondary pericardial infection from an open percutaneous window was noted by Williams and Soutter who found that pericardial windows were not suited for prolonged use when the pericardial fluid is sterile as seven of their eleven patients became secondarily infected.

Complications of pericardiocentesis generally had been thought to be infrequent until the appearance of the review by Kilpatrick and Chapman[6] in which they reported upon twelve patients who had 20 pericardial taps. A cardiac chamber was entered in seven of the twelve resulting in hypotension and tachycardia in three of the patients. One death occurred after instillation of nitrogen mustard into the pericardial space of a patient with metastatic carcinoma. They concluded that pericardiocentesis is indicated only in cases of progressive cardiac tamponade. The only other examination of the complications of pericardiocentesis in the modern literature is an anecdotal study by Kotte and McGuire[7] who reported that "16 of 21 highly skilled and experienced cardiologists and cardiovascular surgeons have seen . . . at least one fatality due to or following upon blind pericardial paracentesis."

Pericardial window and pericardial biopsy are useful diagnostic and therapeutic tools, but have a significant morbidity. The purpose of this report is to provide a comparison between two methods of diagnosing and treating pericardial effusions—a percutaneous pericardial window technique and pericardiocentesis.

In this series seven of the 20 patients with percutaneous pericardial windows developed postoperative atelectasis and pleural effusions due to splinting and poor respiratory effort on the left side. Six of the patients who initially had sterile pericardial fluid but in whom Penrose drains were left in place developed secondary infections. Percutaneous pericardial drains were routinely left in place to promote further pericardial drainage. These should probably not be routinely left in place after diagnostic pericardial biopsy except with purulent effusions or recurrent tamponade, since the infection rate was increased in the patients with drains. Two patients developed bilateral lower lobe pneumonia requiring endotracheal intubation and protracted hospitalization. The diagnostic yield from the 20 biopsies was

Table II Complications of pericardial windows—13 patients

	No of patients
Secondary infection	8
Atelectasis and pleural effusion	7
Chronic sinus tract	4
Pneumothorax	2
Pneumonia with respiratory failure	2
Pneumonia	1
Atrial flutter	1

Table III Pericardial windows Organisms recovered

Organism	Primary isolate 4 patients	Secondary isolate, 8 patients
Escherichia coli	2	
Haemophilus influenzae	1	
Coagulase-positive staphylococci	1	3
Proteus species	1	2
Pseudomonas aeruginosa	1	6
Klebsiella pneumoniae	1	4
Enterococci		2

the surgical procedure One death was due to acute myocarditis and another was due to a pericardiocolic fistula from a recent gunshot wound

The eight patients (40 per cent) who developed secondary wound or pericardial infections had enteric organisms or coagulase positive staphylococci cultured from the purulent drainage (Table III) They all had fever which lasted from five days to three weeks. Their peripheral leukocyte counts ranged from 12 000 to 32 000 per cubic millimeter during the time clinical features suggested infection Four patients developed chronic draining sinus tracts after performance of the pericardial window One patient developed a sinus tract which did not close for 6 months after the procedure The patients with secondary infections all had protracted hospitalizations—an average of 42 days after the window procedure compared to an average of 20 days for the patients who had the procedure without a secondary infection

In seven patients a pericardial window was performed to drain a purulent effusion In four of these patients organisms were cultured from the pericardial fluid obtained at the time of surgery The organisms cultured were *Escherichia coli Haemophilus influenzae* and coagulase-positive staphylococci and one patient had *Escherichia coli* Proteus species *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* (Table III) One patient had a sterile effusion but had received penicillin for pneumococcal pneumonia during the five days prior to performance of the pericardial window Of interest were two of the patients who had a pericardiocentesis prior to the window and biopsy procedure The pericardial fluid obtained from the pericardiocentesis eventually cultured *Histoplasma capsulatum* from one patient and *Mycobacterium tuberculosis* from another The window was performed to drain the pericardium after purulent fluid was obtained in both instances.

Pericardiocentesis During the same four year period (1966 to 1969) 21 patients had pericardioceteses. The mean age was 38 years, with a range of 1 to 82 years. Two patients had ventricular punctures and one had an atrial puncture determined by electrocardiographic monitoring with the use of the needle as the exploring electrode.[4] There were no complications from any of these myocardial punctures The final clinical diagnoses in these 21 patients are shown in Table IV In four instances an etiologic diagnosis of purulent pericarditis was made from the pericardial fluid The organisms cultured were (1) *Haemophilus influenzae* (2) *Diplococcus pneumoniae* (3) *Histoplasma capsulatum* and (4) *Mycobacterium tuberculosis* Of interest was the finding of a nonspecific pericarditis on biopsy which was sterile in the patient who grew *Histoplasma capsulatum* from the pericardiocentesis fluid The patient who eventually cultured *Mycobacterium tuberculosis* had a biopsy which disclosed noncaseating granuloma. The biopsy findings allowed early institution of antituberculosis therapy

Ten of the 21 patients who had pericardioceteses later had a percutaneous peri

Selective cine coronary arteriography and vectorcardiographic diagnoses: Correlative study of one hundred patients

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The usefulness of the vectorcardiogram (VCG) in the clinical diagnosis of coronary artery disease is an unsettled question. Recent work with a theoretic computer model of the myocardium by Selvester and associates[1,2] suggests that the magnitude and location of myocardial scars may be determined with reasonable accuracy by changes in the conventional spatial VCG.

Since cine coronary arteriography[3] provides relatively accurate visualization of the coronary arteries during life, this technique was used to judge the efficacy of the VCG in detecting the severity and distribution of coronary artery disease. We have reviewed the records of 100 patients who had selective cine coronary arteriography and VCG's, and have statistically correlated VCG diagnoses of myocardial infarcts with arteriographic changes in the coronary arteries.

Methods

One hundred consecutive cases were selected from records of the Cardiovascular Department, Hospital of the Good Samaritan Medical Center covering a 20 month period. Patients with the following disorders were not considered: (1) endocardial or pericardial disease, (2) myocardial diseases, including rheumatic heart disease, myocarditis, and cardiomyopathies, (3) congenital heart disease, (4) arterial hypertension, (5) previous cardiovascular surgery, (6) significant anemia or polycythemia, and (7) metabolic disorders, including diabetes mellitus. Seventy per cent of the patients were male. Subjects were between 37 and 62 years of age except for the youngest patient, age 19, and the oldest, age 70.

All patients included in this study had selective coronary arteriography and a VCG. Cineangiocardiograms were obtained with good visualization in the anteroposterior (AP) and right and left oblique projections, before and after administration of nitroglycerin.

Selective coronary arteriography was performed by the conventional Sones technique[3] with a six-inch Thompson Huston tube mounted on a General Electric C arm. Left ventriculograms were obtained in the AP and right oblique projections.

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surprisingly poor—one tuberculous pericarditis and one fibrosarcoma.

The complications of the pericardiocenteses were ventricular and atrial punctures which were not associated with any morbidity. Diagnoses were obtained primarily from the pericardial fluid in three of 21 patients: two with purulent pericarditis and one with histoplasmosis. It should be noted that pericardial effusion is not an uncommon finding in patients with congestive heart failure who have no pericardial disease[8] and in patients with hypertension without congestive failure. Four of the 20 patients who had pericardial windows had only hypertensive and ischemic heart disease with congestive heart failure as the final diagnosis. These patients are poor operative risks and should be evaluated for diagnostic procedures only after they are fully compensated. In view of the significant morbidity and poor diagnostic yield from percutaneous pericardial windows, we would propose the following recommendations.

Indications

I. Indications for percutaneous pericardial windows
   A. Drainage for purulent pericardial effusions
   B. Recurrent tamponade after one pericardiocentesis
   C. Pericardial biopsy in chronic effusions after an unproductive pericardiocentesis
II. Indications for pericardiocentesis
   A. To relieve tamponade
   B. To establish the etiology of a pericardial effusion, particularly to evaluate the possibility of purulent pericarditis

A pericardial effusion should not be tapped in the presence of congestive heart failure except for the indications of II A and B above.

The percutaneous pericardial window technique in the present series was associated with a high complication rate primarily because of secondary infections (40 per cent) due to the prolonged open percutaneous drainage; therefore, the indications for a pericardial window with prolonged percutaneous drainage should be carefully considered before recommending the surgical procedure.

Summary

The hospital records of 20 patients admitted to Parkland Memorial Hospital in Dallas with pericardial effusion during the four year period of 1966 to 1969, and who underwent pericardiocentesis and percutaneous open pericardial windows, were reviewed. The etiologies of the effusions were as follows: purulent pericarditis (5), hypertensive and ischemic heart disease with congestive heart failure (4), and chronic idiopathic effusion (4). Specific etiologic diagnoses were made from the pericardial biopsy in only two cases (10 per cent), while 13 (65 per cent) had at least one serious complication in the postoperative period with eight (40 per cent) developing secondary infection. Twenty-one patients underwent pericardiocenteses without complications and four etiologic diagnoses (20 per cent) were made. Suggestions for indications for these procedures are presented.

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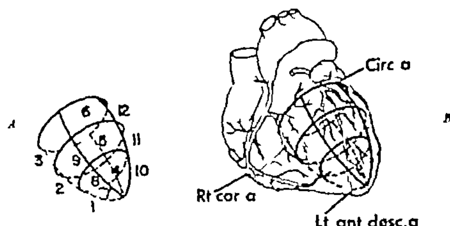


Fig. 2. A, Twelve subdivisions of left ventricle and interventricular septum used in this study. Anteroseptal subdivisions: 1, apical; 2, midregion; 3, basal. Superior subdivisions: 4, apical; 5, midregion; 6, basal. Inferior subdivisions: 7, apical; 8, midregion; 9, basal. Posterior subdivisions: 10, apical; 11, midregion; 12, basal. B, Myocardial subdivisions outlined prominently with superimposed coronary arterial circulation.

Table II. Proposed coronary artery distribution to myocardial subdivisions

Coronary artery	Myocardial subdivisions											
	Anteroseptal			Superior			Inferior			Posterior		
	1	2	3	4	5	6	7	8	9	10	11	12
Right coronary							X	X	X			
Left anterior descending	X	X	X	X	X	X	X			X		
Circumflex						X				X	X	X

"X" indicates subdivisions perfused by respective coronary artery.

example, the right coronary artery supplies most of the inferior surface of the heart (part of subdivision 7, all of 8 and 9). Therefore, hemodynamically significant coronary disease in the proximal right coronary artery would be expected to produce myocardial damage primarily in subdivisions 7, 8, and 9. Investigation of the efficiency of the VCG in localizing the site of myocardial lesions was based on these assumptions.

Results

Normal coronary arteries. Table III summarizes the findings in 40 patients with normal coronary arteriography. The VCG in 8 of the 40 patients indicated Type IV infarcts. Types I, II, and III lesions were suggested by the VCG in 16 patients. The remaining 16 patients with normal coronary arteries had normal VCG's.

Normal VCG's. Twenty-five patients in the study group of 100 had normal VCG's and are summarized in Table IV. Sixteen of these 25 patients had normal coronary arteriograms. Six patients had severe atherosclerotic disease in one artery (75 to 100 per cent narrowing or occlusion), one had severe disease in two arteries, and two patients had severe disease in three arteries. Seven patients of the 25 with normal VCG's had minimal diffuse irregularities of the QRS-E loop which were not considered significant.

Correlation of VCG with coronary arteriography. Table V indicates a statistically sig

*Table I. Proposed VCG criteria for myocardial infarcts and/or fibrosis**

	Type and description of lesion	Estimate of diameter of lesion (cm)	Magnitude on QRS-E loop (mv)	Duration on QRS-E loop (msec)
I	Single small	1 0-1 4	0 08-0 13	4-6
II	Two or more small	1 0-1 4	0 08-0 13	4-6
III	Medium	1 5-3 0	0 14-0 20	7-15
IV	Large (or Type III lesions in contiguous subdivisions)	>3 0	>0 20	16-30

*Each infarct suspected by VCG represents lesion in frontal, horizontal, and sagittal projections. Estimate of infarct size is based on the theoretic analogue computer model of the myocardium. Type IV lesions represent infarct in the major portion of one or more subdivisions. Type III infarct in contiguous subdivisions are equivalent to single Type IV infarct.

Cine coronary arteriograms were reviewed by one of us (E. J. E.). Atherosclerotic narrowing of the coronary lumen was graded in four classifications: 10 to 25, 25 to 50, 50 to 75, and 75 to 100 per cent. Severe coronary disease represents greater than 75 per cent narrowing or complete occlusion of the arterial lumen. Moderate coronary disease indicates arterial narrowing of between 50 and 75 per cent of the lumen.

Vectorcardiographic tracings were recorded with a Hart PV 3 amplifier and oscilloscope. The Cube system of electrode placement was employed. Spatial and timed VCG's were recorded at a speed of 50 mm. per second in the horizontal, frontal, and right sagittal projections. VCG's were obtained routinely 24 hours prior to coronary arteriography.

Vectorcardiographic interpretations were made by one of us (R. H. S.) without knowledge of the arteriographic findings or clinical histories. Two cases in which the vectorcardiographer could not distinguish between right ventricular hypertrophy and posterior wall infarction were not included in the study.

VCG's were interpreted with the use of accepted criteria for diagnosis of myocardial infarcts[4,5] and our proposed method for the diagnosis of small lesions.[1,6] Smaller lesions appear in the VCG as "scallops" which distort the smooth progression of the normal QRS-E loop and are measured by voltage (millivolts) and time (milliseconds).[6] The size of the lesion is demonstrated by projecting a line across the scallop in the path that the VCG loop would have taken had it not departed

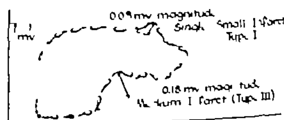


Fig. 1. Horizontal plane vectorcardiogram illustrating method of plotting myocardial lesions from scallop deformities in QRS-E loop.

from a normal smooth progression (Fig. 1).

Suspected abnormalities in the VCG were divided into four groups according to voltage and time changes in the QRS-E loop (Table I). Type I lesions are single small deviations from the QRS-E loop. Type II lesions are two or more small deviations. Type III scars are single medium deviations. Type IV lesions are single larger deviations (or two Type III lesions in contiguous subdivisions) and correspond to the accepted vectorcardiographic criteria for myocardial infarcts.[4,5]

The *myocardium* was divided into 12 subdivisions modified from the computer model of Selvester and associates[1,3] (Fig. 2, *A*). An activation sequence in the heart similar to that reported by Scher and Young[10] and Durrer and associates[11] is the basis of this model.

It was impossible to consider individual differences in coronary anatomy for such a large series of patients and therefore necessary to make certain assumptions regarding which myocardial subdivisions were generally perfused by each coronary artery. Fig. 2, *B* and Table II illustrate the proposed distribution of each major coronary artery to the 12 subdivisions of myocardium. For

Table VII. Correlation of severe coronary artery disease with location of VCG Type IV infarcts

*Coronary arteriographic diagnosis**	*No. of VCG Type IV lesions†*			
	7–9‡	*1 7 10*	*6 10–12*	*Totals*
Severe disease in right coronary artery	11§	12	3	20
Severe disease in left anterior descending artery	8	13	3	24
Severe disease in circumflex artery	7	5	2	14
Totals	20	30	8	58

*Severe coronary disease is defined as 75 to 100 per cent narrowing or occlusion of the arterial lumen.
†N = 58; χ^2 = 2.33; P > 0.05.
‡Numbers at heads of columns represent myocardial subdivisions used in computer model of the heart.
§Figures in bold face type indicate myocardial subdivision perfused by respective coronary artery (see Fig. 2, C and Table II).

Table VIII. Correlation of moderate to severe coronary artery disease with location of VCG Types I, II, and III lesions

*Coronary arteriographic diagnosis**	*No. of VCG Types I, II, III lesions†*			
	7–9‡	*1 7 10*	*6 10–12*	*Totals*
Disease in right coronary artery	12§	12	13	37
Disease in left anterior descending artery	5	10	8	23
Disease in circumflex artery	7	7	8	22
Totals	24	29	29	82

*Moderate to severe coronary disease is defined as 50 to 100 per cent narrowing or occlusion of the arterial lumen.
†N = 82; χ^2 = 2.71; P > 0.05.
‡Numbers at heads of columns represent myocardial subdivisions used in computer model of the heart.
§Figures in boldface type indicate myocardial subdivisions perfused by respective coronary artery (see Fig. 2, C and Table II).

the value of the VCG in this regard by comparing arteriographic changes in the coronary vessels with vectorcardiographic evidence of myocardial infarcts and/or fibrosis.

Correlative pathological studies[11-14] indicate that conventional VCG criteria are 90 per cent accurate[14] in predicting the presence of large myocardial infarcts and 70 per cent reliable[3,11,12] in localizing infarcts. Generally accepted vectorcardiographic criteria for myocardial infarcts[3] involve major distortions in the VCG loop and usually identify only large areas of myocardial necrosis or fibrosis. VCG interpretations which consider smaller deviations in the QRS-E loop might be useful in identifying smaller areas of myocardial scarring.

Burch and colleagues[1] were the first to suggest that small changes ("arcs") in the VCG loop were related to small myocardial scars. They proposed no specific criteria for interpreting these minor alterations in the QRS-E loop. Recent work with a theoretic computer model of the electrical field of the heart[2,4] indicates that it may now be possible to define the size and location of such small lesions. Specific VCG criteria for diagnosis of small lesions which are outlined in this study, using the computer model as a guide, were previously reported.[9]

Experimental evidence[16] indicates that myocardial necrosis occurs only with the coronary lumen narrowed by 50 per cent or more. Increases in stenosis over 50 per cent produce disproportionately greater hemodynamic effects. Mild coronary nar-

Table III Forty patients with normal coronary arteriograms

VCG diagnosis	No of patients
Normal	16
Type IV lesions	8
Types I II and III lesions	16
Total	40

Types I II and III lesions are not tabulated when associated with Type IV infarct in the same patient.

Table IV Twenty five patients with normal vectorcardiograms

Coronary arteriographic diagnosis	Patients with normal† VCG
Normal coronary arteries	16
Severe disease in one artery	6
Severe disease in two arteries	1
Severe disease in three arteries	2
Total	25

*Severe coronary disease is defined as 75 to 100 per cent narrowing or occlusion of the arterial lumen.
†QRS-E loop in seven patients demonstrated minimal irregularities which were considered to be within the limits of normal.

nificant correlation between VCG diagnoses of Type IV infarcts and severe coronary arteriographic changes (75 to 100 per cent narrowing or occlusions) VCG Type IV infarcts were identified in 12 of 29 patients with severe disease in one artery in 10 of 14 patients with severe disease in two arteries and in 2 of 7 patients with severe disease in three arteries.

Table VI shows no correlation of moderate to severe coronary disease (50 to 100 per cent narrowing or occlusion) with VCG diagnoses of small and medium lesions (Types I II and III) VCG Types I II and III lesions were present in 16 of 32 patients with normal coronary arteries, in 8 of 11 patients with moderate to severe coronary disease in one artery in 10 of 15 patients with moderate to severe disease in two arteries and in 6 of 8 patients with moderate to severe disease in three arteries

There was no significant statistical correlation between the localization of myocardial infarcts by VCG and the site of coronary narrowing as indicated in Tables VII and VIII

Table V Correlation of severe coronary artery disease with VCG Type IV myocardial infarcts

Coronary arteriographic diagnosis	No of patients with VCG diagnosis†	
	Type IV infarcts	Normal and Types I II III lesions
Normal coronary arteries	8	32
Severe disease in one artery	12	17
Severe disease in two arteries	10	4
Severe disease in three arteries	2	5
Totals	32	58

*Severe coronary disease is defined as 75 to 100 per cent narrowing or occlusion of the arterial lumen.
†N = 90; $\chi^2 = 12.61$; $p < 0.01$

Table VI Correlation of moderate to severe coronary artery disease with VCG Types I II and III lesions

Coronary arteriographic diagnosis*	No of patients with VCG diagnosis†	
	Types I II III lesions	Normal VCG's
Normal coronary arteries	16	16
Disease in one artery	8	3
Disease in two arteries	10	5
Disease in three arteries	6	2
Totals	40	26

Moderate to severe coronary disease is defined as 50 to 100 per cent narrowing or occlusion of the arterial lumen.
†N = 64; $\chi^2 = 3.11$; $p > 0.05$.

Discussion

The usefulness of the VCG in the diagnosis of coronary artery disease is unresolved It was our intention to investigate

Summary

One hundred patients were studied with cine coronary arteriography and vector cardiograms (VCG's). Coronary artery narrowing was estimated and correlated with vectorcardiographic diagnoses of myocardial infarcts and/or fibrosis. An anatomically and physiologically derived computer model of the myocardium was used as a means of interpreting the spatial VCG with regard to the size and site of destructive lesions with a 12 myocardial subdivisions.

Standard VCG criteria for large myocardial infarcts as well as new criteria for identification of smaller lesions were compared with coronary arteriographic findings. Myocardial lesions were identified as scallops in the QRS-E loop and their size was estimated by the magnitude and duration of deviation from a smooth progression of the VCG loop.

A significant statistical correlation was found between the presence of severe coronary artery disease and vectorcardiographic evidence of large myocardial infarcts. VCG diagnoses of small and medium lesions had no statistical correlation with hemodynamically significant coronary artery disease.

There was no significant statistical correlation between coronary arteriographic findings and VCG localization of infarcts. This is most likely due to anatomical variation in regional arterial supply and collateral vessel formation and is supported by a previous observation that the degree of coronary arteriographic change is inconsistent with the degree of ventricular dysfunction as demonstrated by ventricular angiograms.

The VCG appears to be a useful clinical adjunct in the diagnosis of severe coronary artery disease and large myocardial infarcts. However there is no evidence that smaller lesions predicted by VCG relate to the size or location of small scars in the myocardium.

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rowing (less than 50 per cent) generally should not produce myocardial scarring but hemodynamically significant arterial lesions (greater than 50 per cent) may result in myocardial destruction.

Complete occlusion or severe narrowing (75 to 100 per cent) of a major coronary artery may produce large infarcts easily detected by the VCG. Such myocardial scarring would correspond to our VCG Type IV lesion. Smaller (Types I, II, and III) scars also could occur in the presence of severe coronary disease.

Pathological studies[18,19] indicate that major coronary artery occlusion produces a myocardial infarct in more than 50 per cent of cases. In those instances in which myocardial infarcts are not associated with complete coronary occlusion, severe coronary atherosclerosis is invariably present. Baroldi and Scomazzoni[19] found that in about one fifth of cases the presence of myocardial infarction was not directly related to the degree of narrowing in the major vessels perfusing the involved segment. This raises the possibility that the VCG changes observed might relate more specifically to ventricular function as seen on ventriculograms. Large myocardial infarcts (Type IV) might be expected to be associated with an akinetic or dyskinetic segment, although this would be less likely in Types I, II, and III. This hypothesis is the basis of a recent report.[21] In that study both the McFee corrected lead system and the Cube lead system were used and poor correlation of the VCG with coronary artery anatomy was observed with both methods. Type IV lesions were associated with cine ventriculograms demonstrating akinetic or dyskinetic segments with a 90 per cent probability. These lesions were localized within 1 cm. and the size predicted within 1 cm. with an 85 per cent reliability.

Severe coronary arteriographic changes correlated well with the presence of VCG Type IV infarcts (Table V). This finding supports the generally accepted[1-4] conclusion that major distortions in the QRS-E loop represent large areas of myocardial destruction.

The poor correlation between small to medium VCG infarcts and moderate to severe coronary disease in this study indicates that attaching significance to smaller deviations in the QRS-E loop as indicators of coronary pathology is not justified. However, certain theoretic inconsistencies may exist in the proposed VCG criteria for small infarcts. For example, large activation fronts which are present on opposite sides of the heart during the middle of ventricular depolarization may completely neutralize each other. Therefore, two large infarcts occurring on opposing surfaces of the myocardium might produce little or no net change in the appearance of the VCG loop.

The inability of the VCG to reliably predict the site of myocardial scarring may be due to several factors: (1) intrinsic inaccuracy of VCG criteria—pathological studies[8,13,14] show the conventional VCG criteria to be only 70 per cent accurate in predicting the site of myocardial destruction; (2) theoretic inconsistencies in the proposed criteria for infarcts; (3) anatomic variability in the coronary circulation;[22] and (4) presence of significant collateral circulation.

Interestingly, one fifth of our patients with normal coronary arteriography exhibited Type IV infarcts by VCG. False positive VCG interpretations are probably responsible for the diagnosis of infarcts in the absence of coronary disease in some of these patients. Cunnar and associates[8] report 32 per cent false positive VCG diagnoses of infarcts and attribute this discrepancy to confusing QRS-E loop deformities produced by concomitant ventricular hypertrophy or bundle branch block. Anoxia, prolonged tachycardia, sympathomimetic agents, and possibly small vessel coronary disease may explain some instances of significant myocardial destruction associated with normal appearance of the coronary arteries.

Our finding that more than one third of patients with normal VCG's had severe coronary disease may be related to the following: (1) intrinsic inaccuracy of VCG criteria,[9,14] or (2) significant collateral circulation which may leave the myocardium intact in the presence of significant coronary disease.

Summary

One hundred patients were studied with cine coronary arteriography and vectorcardiograms (VCG's). Coronary artery narrowing was estimated and correlated with vectorcardiographic diagnoses of myocardial infarcts and/or fibrosis. An anatomically and physiologically derived computer model of the myocardium was used as a means of interpreting the spatial VCG with regard to the size and site of destructive lesions within 12 myocardial subdivisions.

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The sequential estimation of plasma catecholamines and whole blood histamine in myocardial infarction

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Gazes, Richardson, and Woods,[1] using the ethylenediamine fluorometric method of Weil-Malherbe, examined the plasma of 13 patients with myocardial infarction. Levels were taken at random within the first 36 hours and again after 72 hours. Initially, mean elevations of norepinephrine approximately twice the normal levels were found, with mean epinephrine elevations of approximately three times normal. At the end of 72 hours, norepinephrine levels had returned to the quoted normal for their method, but epinephrine had remained approximately double the normal. There was no attempt to correlate cardiac dysrhythmias with raised catecholamine levels in this study.

Although several workers[2-3] have reported increased urinary catecholamine levels after myocardial infarction, a decade appears to have passed before McDonald and associates, using the trihydroxyindole fluorometric method of Anton and Sayre, further investigated plasma catecholamines. In a series of 50 patients with myocardial infarction they noted a significant increase in the mean plasma level of norepinephrine compared with that of normal control patients. The level of epinephrine in both groups of patients, however, was similar. Further correlation with respect to cardiac dysrhythmias was made. It indicated that patients with atrial or ventricular dysrhythmias in the first five days following infarction had higher norepinephrine concentrations than those patients without dysrhythmias or with ventricular dysrhythmias occurring after five days from the onset of infarction.

In relating whole blood histamine levels to myocardial infarction, there appears to be a single paper by Kipshidze and Barighyan.[5] These authors, using a biological assay with guinea pig small intestine, studied levels in man following myocardial infarction. They noted elevations up to ten times normal and related these increased levels to the development of both chest pain and hypotension.

The present study endeavored to assess sequential changes for 24 hours in plasma catecholamines and whole blood histamine in patients with myocardial infarction.

Methodology

Subjects. Twenty-five men aged 29 to 68 (mean 56) years, who had been admitted to cardiac intensive care units in the hospitals in the Vancouver area with recent myocardial infarction, were investigated.

The presence of myocardial infarction was substantiated in all cases by electro-

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be 86 mm Hg with a range extending from 72 to 100 mm Hg The mean heart rate on initial examination was found to be 90 beats per minute with a range extending from 80 to 100 beats per minute The central venous pressure measured at the initial examination was found to be 12 cm. H_2O with a range extending from 9 to 15 cm H_2O Subsequent measurements of the systolic blood pressure heart rate and central venous pressure are illustrated in Fig 1 The mean urine output was 34 ml per hour in the 24 hour period of study During the period of study four patients showed atrial or ventricular dysrhythmias. Skin vasoconstriction or sweating was not noted in the eight patients. Morphine was given in doses ranging from 30 to 75 mg in the 24 hour period of study Two of the eight patients in this group died

Group C comprised eight patients. The mean systolic blood pressure recorded on initial examination was found to be 124 mm Hg with a range extending from 114 to 134 mm Hg The mean heart rate on initial examination was found to be 84 beats per minute with a range extending from 77 to 91 beats per minute The central venous pressure measured at initial examination was found to be 8 cm H_2O with a range extending from 5 to 11 cm. H_2O Subsequent measurements of systolic blood pressure heart rate and central venous pressure for this group are recorded in Fig 1 The mean urine output in the 24 hour period of study was greater than 60 ml per hour During the period of study one patient showed atrial dysrhythmia. Morphine was administered to six of the eight patients in doses varying from 15 to 60 mg over the 24 hour period One patient in this group died

Laboratory technique Plasma levels of norepinephrine and epinephrine were estimated by a modified trihydroxyindole method which has been evaluated by studies of 50 normal subjects.

Blood from the antecubital vein was collected in a polypropylene tube containing ethylene diamine tetra-acetic acid (EDTA) the protein precipitated by perchloric acid, and after centrifugation the catecholamines adsorbed onto aluminum oxide. Elution from the aluminum oxide was performed with perchloric acid and the eluate centrifuged at high speed to remove the fine particles of aluminum oxide which may interfere with subsequent fluorescence Differential analysis of norepinephrine and epinephrine was effected through the use of their optimum pH levels of 6 5 and 4 0 respectively and by their different excitation and emission wavelength bands. The activation wavelengths of 380 and 425 nm and fluorescence wavelengths of 480 and 500 nm for norepinephrine and epinephrine respectively were used The fluorescence of the samples was determined by the use of an Aminco-Bowman spectrophotofluorometer (American Instrument Co.) which is equipped with a xenon lamp in an off-axis ellipsoidal condensing system

Whole blood histamine was determined by a modification of the fluorometric procedure of Anton and Sayre[7] An aliquot of the blood drawn for catecholamine estimation was transferred into an iced test tube This was treated with concentrated perchloric acid and histamine extracted from the supernatant fluid by the stated procedure. Fluorophor formation with orthophthaldialdehyde (OPT) and citric acid stabilization of the fluorescence intensity was performed. The fluorescence intensity of the histamine-OPT complex was measured in the Aminco-Bowman spectrophotofluorometer in the same manner as the catecholamines An activation wavelength of 358 nm, and an emission wavelength of 450 nm were used.

Results

The mean levels of plasma catecholamines established in 50 healthy subjects taken in the resting fasting state were as follows norepinephrine 0.24 ng per milliliter with a range of 0 15 to 0.33 ng per milliliter epinephrine 0 04 ng per milliliter with a range of 0.00 to 0 08 ng per milliliter The mean level of whole blood histamine established in the same group of healthy subjects was 0 052 μg per milliliter with a range of 0 015 to 0 089 μg per milliliter The levels of norepinephrine in 25 patients who had been 24 hours in the coronary monitor unit but did not have a clinically proven infarction were 0.29 ng per milliliter with a range of 0.23 to 0.35

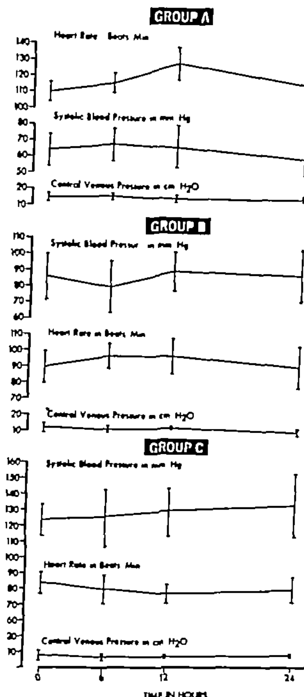


Fig. 1. Relation of central venous pressure, heart rate, and systolic blood pressure to time in the three clinically defined groups.

cardiograph (W.H.O. designation) and the characteristic pattern of evolution of the three serum enzymes ATP:creatine phosphotransferase (2.7.3.2), L-aspartate:2-oxoglutarate aminotransferase (2.6.1.1) and L-lactate:NAD oxidoreductase (1.1.1.27).

Normal control subjects were 50 individuals in the resting state who were considered to be average healthy persons, all with a normal heart rate and blood pressure. Twenty-five persons admitted with a suspicion of myocardial infarction and treated in the same cardiac intensive care units as those patients with proved infarction were also studied.

Blood samples from the patients with electrocardiographically confirmed infarctions were taken on admission to the intensive care unit and at approximately 6, 12, and 24 hours thereafter.

These patients were divided retrospectively into three groups on the basis of their clinical presentation and progress. Blood samples from the patients with suspected myocardial infarction were taken approximately 24 hours after admission to the intensive care unit. Clinical shock was defined by the measurements available: a systolic blood pressure of less than 100 mm. Hg, a heart rate greater than 100 beats per minute, a urinary output of less than 20 ml. per hour, a central venous pressure greater than 15 cm. H_2O, and, finally, cold sweating extremities.

Group A comprised nine patients who were considered to be in clinical shock. The mean systolic pressure recorded on initial examination was 64 mm. Hg with a range extending from 53 to 75 mm. Hg. The mean heart rate on initial examination was found to be 110 beats per minute, with a range extending from 104 to 116 beats per minute. The central venous pressure measured at the initial examination was found to be 15 cm. H_2O with a range extending from 13 to 17 cm. H_2O. The subsequent mean and range for systolic blood pressure, heart rate, and central venous pressure are recorded in Fig. 1. The mean urine output over the first 24 hours of observation was 16.5 ml. per hour. During the 24 hour period of study, eight patients showed atrial or ventricular dysrhythmias, and it was also noted that all patients showed evidence of skin vasoconstriction with cold, sweating extremities. Eight of the nine patients in this group received doses of morphine varying from 30 to 90 mg. in the 24 hour period of study. Seven of the nine patients in this group died.

Group B comprised 8 patients, but these could not be considered to be in clinical shock on the basis of the criteria previously selected. The mean systolic pressure recorded on initial examination was found to

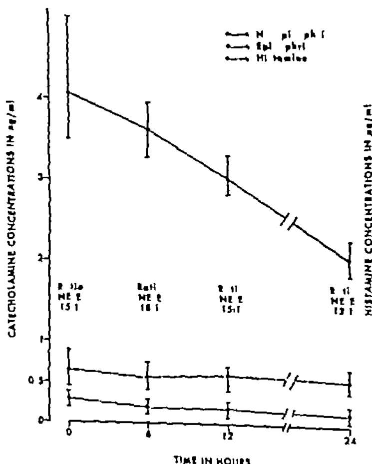


Fig. 2 Group A, relation of levels of catecholamines and histamine to time over the first 24 hours. Normal resting NE, 0.24 ± 0.09 ng. per milliliter normal resting E, 0.04 ± 0.04 ng. per milliliter normal resting histamine, 0.052 ± 0.037 µg per milliliter

cates the striking relationship of cardiac arrhythmias to elevations predominantly of norepinephrine but, to a lesser extent, epinephrine In 12 of the 25 patients no significant dysrhythmias were found atrial dysrhythmias occurred in five, and ventricular dysrhythmias in eight. The five patients with atrial dysrhythmia showed a mean initial norepinephrine level of 3 74 ng per milliliter with a range of 3 22 to 4 26 ng per milliliter The eight patients with ventricular dysrhythmia showed a mean initial norepinephrine level of 3 94 ng. per milliliter with a range of 3 42 to 4 46 ng per milliliter

Discussion

Plasma levels of norepinephrine were found to be significantly elevated in the first 24 hours following myocardial infarction the degree of elevation appearing to have prognostic significance. There was a smaller but significant increase in epinephrine levels. There was no statistically significant increase in whole blood histamine levels. This study therefore, reports the preferential release of norepinephrine over epinephrine in myocardial infarction both in patients with clinical shock and in those in whom clinical shock was not defined The degree of elevation of the catecholamines, particularly norepinephrine, appears to be related to the development of the clinical shock.

An increase in plasma catecholamine levels has been noted in many forms of shock. There have been many experimental studies (in animals) in septic shock, in hypovolemic shock, and in anaphylactoid shock. These have been fully surveyed by

Table I Relation of clinical groups to mean initial amine levels

Clinical group	*Mean initial amine levels*		
	Norepinephrine (ng./ml.)	*Epinephrine (ng./ml.)*	*Histamine (µg/ml.)*
A	4.1 ± 0.6	0.27 ± 0.10	0.064 ± 0.070
B	1.5 ± 0.4	0.12 ± 0.06	0.056 ± 0.030
C	0.61 ± 0.22	0.09 ± 0.04	0.045 ± 0.035
Patients without myocardial infarction	0.29 ± 0.06	0.08 ± 0.04	0.054 ± 0.030

*See legend under Fig. 2 for normal resting levels.

ng. per milliliter. The mean level for epinephrine was 0.08 ng. per milliliter with a range of 0.04 to 0.12 ng. per milliliter. The mean level for whole blood histamine in these patients was 0.054 µg per milliliter with a range of 0.024 to 0.084 µg per milliliter (see Table I).

Figs. 2, 3, and 4 indicate graphically the mean plasma levels of norepinephrine, epinephrine, and whole blood histamine over the 24 hour period of study for the three clinically defined groups A, B, and C. In all groups there appears to be initial elevation at the first point of assay, but subsequent assays indicate a progressive fall in norepinephrine and epinephrine levels over the time period studied. The whole blood histamine levels appear unchanged both on initial assay and during further assays during the period studied.

In Group A, carrying the highest mortality rate, there was significant elevation of norepinephrine ($P < 0.001$) and also of epinephrine ($P < 0.001$), but no significant elevation of whole blood histamine when compared to the normal resting values. This significant elevation of norepinephrine and of epinephrine also occurs when the values are compared to the control group of patients in the cardiac monitor unit without myocardial infarction.

In Group B, with a lower mortality rate, the elevations of norepinephrine and epinephrine, although considerably less, were still statistically significant ($P < 0.001$) when compared to normal resting values and to the control group of patients in the intensive care unit without myocardial infarction. Again there was no change in whole blood histamine.

In Group C, with the lowest mortality rate, there was a progressive reduction in the mean initial plasma levels of norepinephrine and epinephrine, but both are statistically significant elevations ($P < 0.001$) when compared to normal resting values. The mean initial plasma levels of norepinephrine when compared to those of the patients without myocardial infarction show a statistically significant elevation ($P < 0.001$). The mean initial levels of epinephrine, however, are comparable ($P < 0.01$) to the elevated levels of epinephrine in the patients without myocardial infarction. There was no change in the whole blood histamine in this group.

If norepinephrine levels are compared within the three clinical groups, it is found statistically ($P < 0.001$) that each group shows a significant elevation when compared to one another and to the group of patients without myocardial infarction. For epinephrine levels, however, when the clinical groups are compared to one another, Group A shows a statistically significant elevation when compared to Groups B and C, whereas the recorded elevations in Groups B and C are comparable ($P < 0.01$). If epinephrine levels in Groups B and C are also compared with epinephrine levels in the group of patient controls in the intensive care unit without myocardial infarction, then the levels are found to be comparably elevated ($P < 0.01$).

Table II relates the type of arrhythmias to the initial mean plasma levels and indi

Table II Relation of mean initial amine concentrations with dysrhythmias

	No. of patients	Mean initial amine levels	
		Norepinephrine (μg/ml)	Epinephrine (μg/ml)
No significant dysrhythmias	12	0.96 ± 0.12	0.07 ± 0.03
Atrial dysrhythmias	5	1.24 ± 0.32	0.26 ± 0.11
Ventricular dysrhythmias	8	3.91 ± 0.82	0.27 ± 0.07

*See legend under Fig. 2 for normal resting levels.

constituents, and containing large quantities of ATP in a molar ratio of about 1:4 with the catecholamines. It is estimated in man that cells of the adrenal medulla contain about 80 per cent epinephrine and 20 per cent norepinephrine.[11] Norepinephrine biosynthesis occurs within the postganglionic sympathetic neurone, the amine being also stored within the cell as an identifiable granule. The ATP combination, however, may not be as firm as with epinephrine, and there may be considerable norepinephrine in the cytoplasmic sap.[12] Apart from the adrenal medulla, the catecholamine content of tissues varies greatly, with norepinephrine the predominant amine.[13]

The reasons for the preferential release of norepinephrine reported in this study are unknown, and any comment on the mechanism of release must at this stage be speculative. A possible concept for the release of the catecholamines is discussed by Douglas.[14] He suggests that following the quantal discharge of acetylcholine by neurogenic impulses, a sequence of events beginning with the increased permeability of the outer membrane of the chromaffin cell or sympathetic neurone to calcium is initiated. The inward movement of calcium, accelerated by a similar inward movement of potassium, activates adenosine triphosphatase (ATPase) and releases the contents of the granule. The process of granular release requires a high energy potential, whereas the catecholamine release from the cytoplasmic sap is probably achieved by simple diffusion with little or no energy requirement. Euler[15] has shown that the release of catecholamines is much faster from the nerve granule than from the granule of adrenal origin. In vitro at 37° C., nerve granules release half their norepinephrine in six to eight minutes, while those from the adrenal medulla take about 100 minutes for similar quantal release. Euler further showed that local acidosis would considerably enhance the rate of release. Another possible source of the predominantly norepinephrine elevation, at least in the initial phase, is the myocardium with its rich sympathetic innervation. It is calculated that each gram of myocardium contains 0.64 μg of norepinephrine. The release of norepinephrine is presumably initiated by acute tissue hypoxia.

The emotional response to the stress of myocardial infarction and subsequent treatment in an intensive care unit may be considered to be responsible for some of the catecholamine release. That noted in those patients without myocardial infarction but subjected to the stress of hospitalization in the intensive care unit appears to be one of epinephrine rather than norepinephrine. McDonald[4] noted a similar epinephrine release phenomena in six patients undergoing cardiac catheterization, and Levi[16] has shown in studies with subjects undergoing stress with emotional disturbances the release as reflected in urinary catecholamines to be predominantly epinephrine.

A major mechanism of removal from the plasma is reuptake by the granule. Iversen[17] has shown that uptake by the medullary granule is slow compared with that of the nerve granule, but there may be also two different uptake mechanisms for exogenous norepinephrine dependent on the circulating norepinephrine concentration. McDonald[4] has suggested that epinephrine release is short lived, possibly inferring that

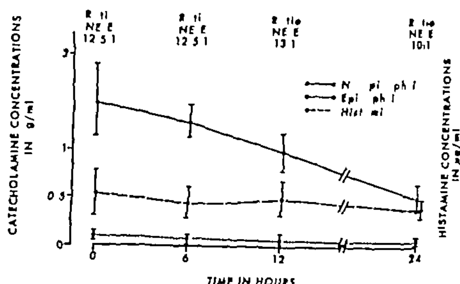


Fig 3 Group B relation of level of catecholamines and histamine to time over the first 24 hours. See legend under Fig 2 for normal resting levels.

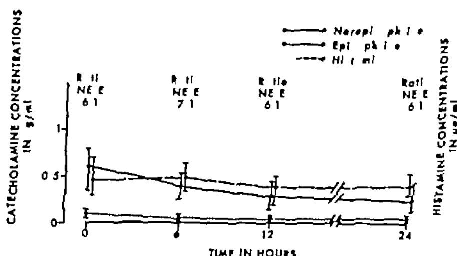


Fig 4 Group C relation of level of catecholamines and histamine to time over the first 24 hours. See legend under Fig 2 for normal resting levels.

Richardson.[8] In such studies, a definite evolving differential release pattern of catecholamines has been noted but this tends to vary with the species and the results obtained are difficult to compare with those obtained in man in whom there is limited information regarding plasma catecholamines in myocardial infarction. The paper of Gazes suggests that epinephrine is the dominant catecholamine during the period of assay extending over 72 hours, whereas McDonald suggests in single assays that norepinephrine solely is released with no detectable elevation of epinephrine. With regard to blood histamine, the single paper of Kipshidze and Barighyan[8] suggests that histamine is released and is related to the decrease of arterial blood pressure. We have been unable to confirm the result reported by these authors. A basic difference in methodology exists, in that histamine was assayed in the paper of Kipshidze and Barighyan[8] by a biological method. In spite of reputed selective extraction of the histamine there is reason to believe that the method may not be as specific as the fluorometric technique used in our study.

Norepinephrine and epinephrine are derived from phenylalanine and tyrosine in a well-defined anabolic pathway, the rate-limiting enzyme being tyrosine hydroxylase.[9] The adrenal medulla is the major site for epinephrine biosynthesis but produces some norepinephrine also. Following formation, epinephrine is stored in identifiable granules distinct from other intracellular

within normal limits irrespective of clinical status. It is concluded that the response of the three vasoactive compounds studied to confirmed myocardial infarction was predominantly the release of norepinephrine.

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the useful half life of epinephrine may be less than that of norepinephrine yielding more readily to catabolism by monoamine oxidase and catechol *O* methyl transferase enzyme system

The effect of morphine given to the majority of patients in this study must also be considered Cairnie and colleagues[18] suggested by indirect experiments that morphine prevented the release of norepinephrine from the postganglionic neurones However Gunne[19] administered increasing doses of morphine to rats then estimated their catecholamine secretion in urine There was a prompt increase in both catecholamines the rise maintaining the normal ratio of norepinephrine to epinephrine—norepinephrine being the dominant amine if the dose of morphine were small With large doses of morphine the epinephrine levels showed a marked rise exceeding those of norepinephrine

The relationship of elevated catecholamine levels to atrial and ventricular dysrhythmias is of particular significance although the mechanism of action is not clear Oppenheimer[20] induced experimental myocardial infarction in dogs. He noted that in the group previously given reserpine there was an almost complete absence of ventricular fibrillation when compared to the control group the members of which had not been given reserpine. This observation suggests that catecholamines play an important role in the production of the ventricular arrhythmias.

The mechanism for the fall in both catecholamines in the 24 hour study period is unknown In the more severe cases it may be due to initial degranulation of the norepinephrine-epinephrine stores without resynthesis of the amines in unfavorable cellular conditions such as marked acidosis. This could cause inhibition of the rate-limiting enzyme In those with response to treatment stabilization of the factors causing release may be an effective reason for the decline in amine levels.

Our findings in respect to the catecholamines confirm in part the recent work of McDonald [4] particularly with norepinephrine levels The levels of epinephrine found in our series did not exceed 0 29 ng per milliliter and are comparable to those quoted by McDonald who however quotes the normal mean epinephrine at 0.25 ng. per milliliter This is approximately five times that quoted by other authors who have determined plasma levels.[4,21,22]

Considering the inconsistent and unpredictable alterations in the hemodynamics of the macrocirculation following myocardial infarction these studies are but preliminary communications. It is obvious that there are many complex changes occurring, of which epinephrine and norepinephrine are but part The relationships between plasma or tissue kinins and catecholamines [24] and between kinins, catecholamines, and 5 hydroxytryptamine[25] require further considerable investigation.

Summary

Plasma norepinephrine and epinephrine, together with whole blood histamine, were measured at six hour intervals for a total period of 24 hours after proved myocardial infarction

The values obtained were compared to resting levels in 50 healthy subjects with a mean heart rate of 72 4 beats per minute and a mean systolic blood pressure of 114 mm Hg and to 25 patients with a mean heart rate of 76 2 beats per minute and a mean systolic pressure of 122 mm. Hg These were patients who were in the cardiac intensive care unit but in whom a diagnosis of myocardial infarction was not substantiated

Norepinephrine levels were significantly higher in the patients with proved myocardial infarction the mean initial reading being up to sixteen times the matched resting levels, whereas epinephrine levels showed a relatively smaller increase initially —up to five times the matched resting levels. A similar elevation was noted in the patients with proved myocardial infarction when compared to those patients in the cardiac intensive care unit in whom a diagnosis of myocardial infarction was not confirmed The degree of initial elevation appears to have prognostic significance in spite of a gradual decrease in the 24 hour period of study The degree of initial elevation also appears to be associated with atrial or ventricular dysrhythmias. The levels of whole blood histamine remained

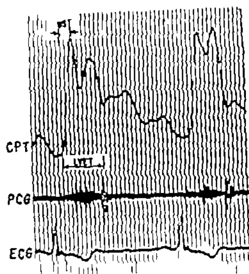


Fig. 1 Typical external carotid pulse tracing seen with IHSS. Time lines = 0.04 second part CPT = carotid pulse tracing; LVET = left ventricular ejection time; PCG = phonocardiogram; UST = upstroke time. Note the UST measurement is the time to achieve the maximum measurement of the *first* peak from the onset of the upstroke in systole. The LVET is measured from the beginning of the upstroke to the dicrotic notch.

inhaled 0.18 c.c. ampules of amyl nitrite and their pulse tracings were recorded for at least 30 seconds following inhalation. Measurement of the dicrotic notch was occasionally difficult at rapid rates following inhalation of amyl nitrite; however, simultaneous phonocardiograms aided the localization of the dicrotic notch by demonstration of the second heart sound. At least four complexes were measured to obtain average values.

The following measurements were made to the nearest 0.01 sec.

1. LVET* was measured as the time from the onset of the steep portion of the carotid pulse tracing to the dicrotic notch (Fig. 1).

2. The increase in LVET was measured following the inhalation of amyl nitrite.

3. The upstroke time (UST) was measured as the time from the onset of the steep portion of the initial rise in the carotid pulse tracing to the maximum peak (Fig. 1). If a bifid pulse occurred, the time to the

*Corrected for rate by the Bazett formula:

$$\text{Corrected value} = \frac{\text{Measured value}}{\sqrt{R-R\ \text{interval (sec.)}}}$$

Table I. Diagnoses following left and right heart catheterization in 158 patients

	Patients
IHSS	23
Pure aortic stenosis	31
Pure aortic insufficiency	11
Aortic stenosis and aortic insufficiency	10
Pure mitral insufficiency	9
Miscellaneous	65
Normal	9

initial peak was utilized. The carotid pulse tracings after inhalation of amyl nitrite were occasionally difficult to record due to subjective discomfort of the patient and the fact that the systolic peak would vary with the position of the transducer. In such instances, the earliest *maximum* peak was utilized to measure the upstroke time.

4. The *ratio* of the UST to the LVET (UST/LVET) was measured before and after the inhalation of amyl nitrite.

The patients all had left and right heart catheterization in the awake state using previously described techniques.[4] Criteria for the diagnosis of IHSS have been listed previously.[4] Table I enumerates the diagnoses. The miscellaneous group comprised patients having single and mixed valvular lesions, congenital heart disease, coronary artery disease, and cardiomyopathies. The normal group consisted of nine patients studied because they manifested bizarre chest pains or other confusing cardiovascular symptoms and signs, but who did not display evidence of cardiac disease.

Results

The LVET before inhalation of amyl nitrite was 0.36 sec. or more in only 7 out of 23 patients with IHSS (Table II). After amyl nitrite inhalation, however, 17 out of 18 patients with IHSS had an LVET of 0.36 sec. or greater (Table II). The ejection time after amyl nitrite inhalation increased to more than 0.06 sec. in 13 out of 18 patients with IHSS and in none of the 53 patients with other disorders (Fig. 2). Two of the 5 IHSS patients who failed to increase their ejection time to more than 0.06 sec. had prolonged ejection times before amyl nitrite inhalation.

Carotid pulse tracings in hypertrophic subaortic stenosis

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Idiopathic hypertrophic subaortic stenosis (IHSS) is a disease of protean manifestations which may mimic many disorders such as valvular aortic stenosis, coronary artery disease, idiopathic myocardial hypertrophy, mitral insufficiency, and psychoneurosis. Definitive diagnosis can be made only by left heart catheterization. Since catheterization is expensive and not without risk, it would be advantageous for the clinician to have a simple screening technique when there is suspicion of IHSS.

The carotid pulse tracing in IHSS has a characteristic bifid contour with a rapid upstroke and a prolonged ejection time.[1] A bifid pulse, however, may also occur in normal patients.[2] The left ventricular ejection time (LVET) is frequently prolonged after inhalation of amyl nitrite.[3] The purpose of the present study was to determine the frequency with which one can expect to detect these abnormalities in IHSS and to assess the specificity of these findings when compared to other cardiac disorders frequently confused with IHSS.

Methods

The carotid pulse tracings of 158 adult patients who had undergone right and left heart catheterization from 1962 to 1970 at Duke University Medical Center were studied. All tracings were recorded on an Electronics for Medicine DR-8 recorder at a paper speed of 75 or 100 mm. per second. An Electronics for Medicine Model A 161 transducer was manually placed on the external carotid artery. A simultaneous phonocardiogram, usually at the left second intercostal space, aided verification of the dicrotic notch by demonstration of the second heart sound. Seventy-two patients

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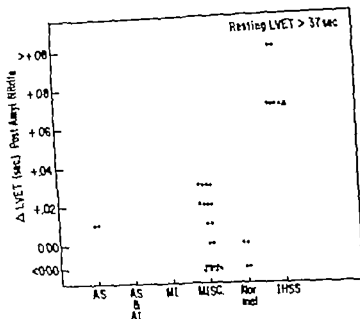


Fig. 2 Changes in LVET following amyl nitrite. AS = aortic stenosis; AI = aortic insufficiency; MI = mitral insufficiency; MISC = miscellaneous; IHSS = idiopathic hypertrophic subaortic stenosis. Thirteen of 18 patients with IHSS had increase in LVET greater than 0.06 sec. as opposed to none of the 53 control patients.

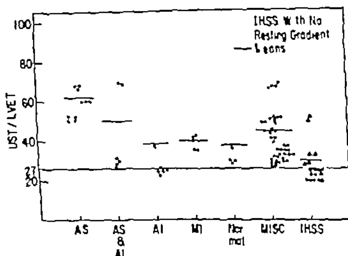


Fig. 3 The ratio of UST/LVET before amyl nitrite in 138 patients. See Fig. 2 for abbreviations. Note that 12 of 23 patients with IHSS had UST/LVET ratios below 0.27. With the exception of aortic insufficiency only 3 of 124 patients without IHSS had UST/LVET ratios below 0.27.

tracing measurements in IHSS and in patients with other disorders.

Out of the 23 patients with IHSS (18 of whom received amyl nitrite) 3 had 3 abnormal values, 9 had 2 abnormal values, 8 had only 1 abnormal value, and 3 had no abnormal values judged by the above criteria (Table II).

Of the three patients (No 9 No 18 and No 20) who displayed none of the above abnormalities, one (No 9) had no resting *left* ventricular systemic artery gradient but presented the typical history—electrocardiogram phonocardiogram and the responses to isoproterenol and to amyl nitrite expected with IHSS. However at the time the pulse tracing was performed the patient was receiving 400 mg of pro-

Table II Individual values obtained by catheterization and external carotid pulse tracings in 23 patients with IHSS

Patient	Before amyl nitrite			After amyl nitrite				Left ventricular systolic outflow gradient (mm. Hg)	
	LVET (sec.)	UST (sec.)	UST/LVET	LVET (sec.)	UST (sec.)	UST/LVET	Increase in LVET (sec.)	Resting	After isoproterenol
1 W P	0 39	0 09	0 23	—	—	—	—	100	—
2. A W	0 34	0 09	0 24	0 40	0 115	0 37	0 07	47	—
3 N A	0 40	0 08	0 20	—	—	—	—	100	—
4 J W	0 33	0 18	0 55	0 40	0 10	0 25	0 07	80	—
5 C. I	0 32	0 09	0 28	0 46	0 10	0 21	0 14	0	131
6. J V	0 37	0 07	0 19	0 44	0 06	0 14	0 07	0	98
7 K. A	0 40	0 08	0 20	0 43	0 06	0 14	0 03	170	—
8. A K.	0 31	0 10	0 32	0 38	0 08	0 21	0 07	0	98
9 F K.	0 28	0 14	0 50	—	—	—	—	0	50
10 J E.	0 32	0 10	0 31	0 40	0 16	0 40	0 08	0	139
11 M W	0 39	0 10	0 26	0 39	0 06	0 16	—	50	—
12 W A.	0 35	0 08	0 23	0 4	0 05	0 12	0 07	90	—
13 H H	0 34	0 09	0 26	0 45	0 07	0 16	0 11	43	—
14 L. S.	0 28	0 15	0 54	0 38	0 10	0 21	0 10	0	70
15 W W	0 33	0 12	0 36	0 41	0 09	0 22	0 08	80	—
16. K. D	0 37	0 10	0 27	0 44	0 04	0 09	0 07	105	—
17 C. M	0 40	0 08	0 20	—	—	—	—	84	—
18. S. M	0 33	0 20	0 62	0 34	0 09	0 27	0 01	0	48
19 M C.	0 30	0 06	0 20	0 39	0 06	0 15	0 09	0	26
20. I T	0 32	0 09	0 28	0 37	0 10	0 27	0 05	0	46
21 N B.	0 33	0 08	0 24	0 39	0 14	0 36	0 06	0	111
22 C. B	0 27	0 11	0 40	0 36	0 04	0 11	0 09	0	50
23 D S.	0 35	0 09	0 26	—	—	—	—	137	—

Fig 3 demonstrates the UST/LVET ratios in the different groups listed in Table I Ten out of 13 patients with IHSS whose resting gradients were over 20 mm Hg had UST/LVET ratios below 0 27 while only 3 out of 124 patients without either IHSS or pure aortic insufficiency had ratios below 0 27 Of these three patients, one had pulmonary hypertension from pulmonary emboli one had an atrial septal defect, and one had an atypical chest pain with normal left and right heart catheterization and normal coronary angiogram Neither isoproterenol nor amyl nitrite was administered during the catheterization of this last patient Four out of nine patients with severe aortic insufficiency (AI) had values below 0 27 No patient with aortic stenosis had a value less than 0 42 No patient with mitral insufficiency had a value under 0 32

The UST/LVET ratio was measured after amyl nitrite inhalation in 72 patients, 18 of whom had IHSS (Fig 4) Eleven of these 18 patients presented UST/LVET ratios of less than 0 23 only 2 out of the remaining 53 patients had ratios in this range Seven out of 10 IHSS patients with resting UST/LVET ratios of 0.27 or more decreased their ratios to less than 0 23 after amyl nitrite inhalation (Table II)

Both IHSS and control patients were evaluated for the presence of the following measurements which were considered abnormal but not necessarily diagnostic for IHSS (1) a resting UST/LVET ratio of less than 0 27 (2) a UST/LVET ratio of less than 0 23 after amyl nitrite inhalation and (3) an increase in LVET greater than 0 06 sec. after amyl nitrite inhalation.

The exact pulse tracing measurements of the 23 patients with IHSS are recorded in Table II Fig 5 indicates the frequency of the following abnormal carotid pulse

been confirmed subsequently by other investigators. Grimberg and colleagues[6] recently attempted to determine the specificity of these findings by comparing the carotid pulse tracings in 50 patients who exhibited IHSS with 287 patients who presented various other cardiac disorders proved by catheterization. Eighty per cent of the patients with IHSS had a combination of a short upstroke and a prolonged ejection time which, with the exception of those patients with aortic insufficiency, was not seen in the other patients evaluated for this combination. Measurements for individual patients were not reported. Our data indicates that the resting carotid pulse tracing is not this specific for the diagnosis of IHSS.

Eleven out of the 23 IHSS patients we studied had resting pulse tracings with a UST/LVET ratio of 0.27 or greater; however, amyl nitrite inhalation produced one of the above abnormalities in 9 of these 11 patients. Thirteen of the 18 patients with IHSS who received amyl nitrite increased their ejection times to more than 0.06 sec. but not one of the 53 control patients had an increase in ejection time greater than 0.03 sec. (Fig. 2). Two of the five patients with IHSS who failed to increase their ejection times significantly (No. 7 and No. 11) displayed abnormally prolonged ejection times initially. Thus pharmacological stimulation with amyl nitrites (or possibly other agents such as isoproterenol or nitroglycerine) is vital to make pulse tracings a sensitive screening device for IHSS.

Cohn and associates[2] noted an increase in ejection time greater than 0.04 sec. in either intra-arterial or external carotid pulse tracings following amyl nitrite inhalation in 11 of 18 patients with IHSS but in only one of 48 patients with other disorders. Cohn used Weissler's regression formula for rate correction of ejection times. Although we used the Bazett formula, our results were similar to Cohn's.

It is established that the left ventricular-systemic artery gradient is increased after amyl nitrite inhalation.[8] Although the mechanism is not clear, several possibilities exist. Wigle and co-workers postulate that the reduced peripheral vascular resistance due to amyl nitrite decreases the aortic outflow orifice due to decreased distending pressure in the ascending aorta. Mason and his associates[11] have demonstrated that atropine induced tachycardia, which was associated with a decreased stroke volume, increased the aortic outflow gradient in IHSS but not in fixed aortic valve stenosis. Decreased venous return to the left ventricle causing increased outflow obstruction in a smaller ventricular chamber is another possible mechanism.[11]

Valvular aortic stenosis and mitral insufficiency most frequently resemble IHSS by physical examination but none of the patients in these two groups had an abnormal UST/LVET ratio. This is expected since aortic stenosis characteristically produces a delayed upstroke and a prolonged ejection time. In mitral insufficiency when aortic outflow obstruction is absent, LVET shortens as stroke volume falls.[12]

Three patients (No. 4, No. 15 and No. 16) with resting gradients had normal carotid pulse tracings; however, amyl nitrite inhalation produced distinctive abnormalities. Since it is established that the resting gradient may be intermittent,[13] it is possible that the gradients were absent at the time the pulse tracings were taken.

Three patients with a diagnosis of IHSS had no abnormality before or after amyl nitrite inhalation. Patient No. 9 had a left ventricular–aortic gradient only after pharmacological stimulation; however, he was receiving 400 mg. of propranolol a day at the time the pulse tracings were recorded. The other two patients (No. 18 and No. 20) had post-premature ventricular beat gradients of 20 to 30 mm. Hg and gradients after isoproterenol of 30 to 50 mm. Hg. It is possible that these two patients possess the muscular disorder of the left ventricle described by Criley and associates[4] as hypertrophic, hyperkinetic cardiomyopathy. This group of patients is prone to produce catheter entrapment after isoproterenol or amyl nitrite; however, Wigle and associates[14] have clearly shown that their ejection times do not increase with amyl nitrite inhalation.

Rapid upstroke times may be seen in severe aortic insufficiency and in idiopathic muscular disease of the left ventricle with no evidence of outflow obstruction. The former groups provide little difficulty in diagnosis since severe aortic insufficiency

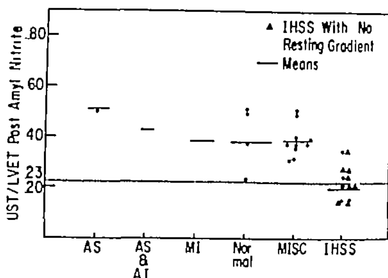


Fig 4 The ratio of UST/LVET after amyl nitrite in 158 patients. See Fig 2 for abbreviations. Note that 11 of 18 patients with IHSS who received amyl nitrite had UST/LVET ratios of less than 0.22 while only 1 of 53 patients with other disorders had ratios in this range

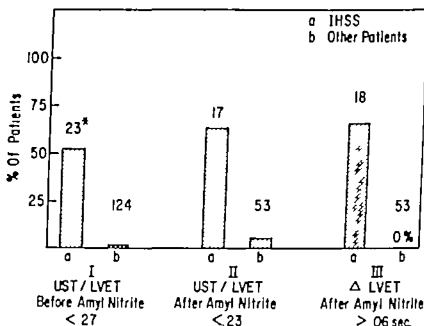


Fig 5 Per cent of patients having a UST/LVET ratio less than 0.27 and 0.23 before and after amyl nitrite inhalation, respectively The right bar graph indicates per cent of patients having an increment in LVET greater than 0 06 sec after amyl nitrite inhalation. (The numerals at the top of the bar graphs indicate the number of patients in each group.) See Fig 2 for abbreviations. The Group B patients evaluated for UST/LVET before amyl nitrite did not include those patients with aortic insufficiency Note that no patient without IHSS had an increase in his LVET after amyl nitrite greater than 0.06 sec.

pranolol a day The other two patients (No 18 and No 20) had left ventricular–systemic artery gradients only after isoproterenol or premature ventricular contractions

Discussion

In this study all of the 12 patients with IHSS whose resting aortic gradients were greater than 20 mm Hg and 5 out of 7 patients who exhibited aortic gradients only after the administering of isoproterenol or amyl nitrite had characteristic carotid pulse tracings exhibiting one or more of these three findings (1) a resting UST/LVET ratio of less than 0 27 (2) a UST/LVET ratio of less than 0 23 after amyl nitrite inhalation and (3) an increase in LVET greater than 0 06 sec after amyl nitrite inhalation

Benchimol[1] described the characteristic rapid upstroke time and prolonged ejection time in the external carotid pulse tracings in IHSS patients these have

Durations and intervals of normal heart sounds in man

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Knowledge of the duration of a heart sound is essential for determination of sound abnormalities including prolongation of sounds and occurrence of short murmurs.

The intervals between the components of a sound and between the sounds themselves are of great importance both for interpretation of the sounds and for recognition of cardiovascular abnormalities.

For these reasons several studies were devoted to these problems in the past. Unfortunately such studies yielded different values according to the technical characteristics of the equipment used and also according to the criteria used for the measurements.

Having at our disposal new equipment, which is able to supply filtered or unfiltered tracings of either displacement, velocity or acceleration,† we thought that a new study would be of importance, both for the values obtained and for comparison with clinical observations.

Method

Our study was made on 23 medical students aged from 21 to 23 years. Fourteen were men, 9 were women. Preliminary physical examinations disclosed normal heart sounds and normal blood pressures. The electrocardiograms (ECG's) of the subjects were normal and their histories did not include significant diseases as far as the heart was concerned.

The equipment used for the study was a new apparatus built by the Research and Development Division of the General Electric Company of Schenectady, N. Y. in collaboration with the staff of our Division. It consists of a piezoelectric displacement microphone, a preamplifier, two differentiating circuits that permit the recording of separate tracings of displacement, velocity and acceleration, a band pass filter, a tape recorder, a booster amplifier, high frequency galvanometers and direct recording on photosensitive paper. The characteristics, results, and

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†These terms should be interpreted as follows: The microphone records data pertaining to the displacement of the chest wall; thus, such a tracing is called a "displacement tracing" (D). The first derivative (dS/dt) of such tracing, electronically obtained, is a tracing of "velocity" (V). The second derivative (d²/dt) is a tracing of acceleration (A).

is rarely if ever found with IHSS Patients with muscular disease usually have a shortened LVET due to low stroke volume and hence a normal UST/LVET ratio It is possible that some patients in this group may have an abnormal UST/LVET ratio An increase in LVET after amyl nitrite inhalation would not be expected

Five of the 124 patients with neither IHSS nor pure aortic insufficiency exhibited one of the above abnormalities Two had right ventricular hypertrophy one had had surgery for an anomalous left coronary artery and two had a normal catheterization One of the patients with a normal catheterization had bizarre chest pain but received no pharmacologic agents during catheterization It is possible that a gradient might have been produced by pharmacologic stimulation Of these five patients without IHSS three received amyl nitrite none of the three had more than one abnormality No patient except those diagnosed as having IHSS had an increase in LVET greater than 0 05 sec after amyl nitrite inhalation Thus our data suggest that for the diagnosis of IHSS either the presence of two of the three above listed abnormalities or an increase in LVET greater than 0 06 sec. is more specific than the presence of a single isolated abnormality This conclusion was vindicated when 14 of the 18 patients who had received amyl nitrite either manifested two of the three abnormalities or exhibited an increase in LVET significantly greater than 0 06 sec.

Summary

Twenty of 23 patients with the diagnosis of IHSS displayed distinctive carotid pulse tracings. Except for those patients with pure aortic insufficiency only 5 of the 124 patients with other cardiac disorders had similar abnormalities These abnormalities were (1) a UST/LVET ratio less than 0 27 before amyl nitrite inhalation (2) a UST/LVET ratio of less than 0 23 after amyl nitrite inhalation and (3) an increase in LVET greater than 0 06 sec after amyl nitrite inhalation

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Table I. Data obtained at the apex (in milliseconds)

	Duration of IV	IV-I	Q-I	Ia-Ib	Ia-Ic	Duration of I	IIA-IIP (splitting)	Duration of II	IIA-os	IIA-III	Duration of III
Velocity, 0-100 Hz											
Mean	63	84	55	32	63	122	29	55	73	141	71
S.D.	17	19	7	7	11	16	5	9	7	30	16
S.E.	4	3	2	1	2	3	1	2	2	5	4
Minimum value	40	60	43	25	50	95	20	40	63	120	45
Maximum value	90	130	70	50	80	170	40	60	90	160	80
Velocity, 40-400 Hz											
Mean			58	30	58	103	23	49	70	132	61
S.D.			7	9	12	16	4	8	6	30	15
S.E.			1	2	2	3	1	2	1	4	8
Minimum value			50	20	43	73	20	35	63	120	40
Maximum value			75	45	90	130	35	65	90	140	80
Velocity, 400-800 Hz											
Mean			66	19		71	15	23			
S.D.			10	9		14	7	11			
S.E.			2	2		3	2	2			
Minimum value			55	10		50	10	10			
Maximum value			85	35		85	30	30			
Acceleration											
Mean			59	26	53	74	23	28			
S.D.			10	6	8	21	6	8			
S.E.			2	1	2	5	1	2			
Minimum value			40	20	35	45	15	20			
Maximum value			80	40	70	140	35	35			

better phonocardiographic system, such study deserved to be repeated.

Intervals

Q-Ia INTERVAL. This interval has special interest because it may become prolonged in clinical conditions. It was found to be longer over the base because of the lack of recording of some early sound vibrations. It was found to be longer in tracings recorded with high filtration for the same reason. Therefore clinical comparison should be made only with our data, recorded either at the apex or at the midprecordium, and excluding the tracings at 400 to 800 Hz. The average values were 55, 58, 59 msec. at the apex and 57, 57, 62 at the midprecordium. The maximum values were 70, 75 at the apex and 60, 75 at the midprecordium for velocity tracings; the maximum value for acceleration tracing was 80 at the apex and at the midprecordium.

Therefore, if one uses a velocity tracing, prolongation of the Q-Ia interval can be stated only *if the interval is longer than 75 msec.* This is somewhat longer than the usually accepted value.

Ia-Ib INTERVAL. This interval measures the distance between the two main high frequency components of the first sound. It was found to be as long as 60 msec. (midprecordium, velocity 0 to 100 Hz) and as short as 10 msec. (apex, velocity 400 *to 800 Hz*). The averages were 32, 30 (apex) and 33, 27 (midprecordium), with shorter intervals for high filtration (19, 20) or acceleration tracings (26, 25).

Ia-Ic INTERVAL. This interval measures the distance between the first and the third component of the first heart sound. Its prolongation should be considered as evidence that there is an "ejection sound" and therefore there is some cardiovascular abnormality. The average figures were 63, 58 (apex), 65, 56 (midprecordium), and 57, 52 (base) for velocity tracings, and 53, 52, 57 for acceleration tracings over the

advantages of this equipment have been presented at a meeting[1-3] and are being published elsewhere in detail[4]

The subjects were in the recumbent position on a cot in a soundproof room The microphone was successively applied to the left fourth intercostal space (i.c.s.) at the midclavicular line (apex) to the left third i c s halfway between the apex and sternal border (midprecordium) and to the left second i c s 2 cm from the sternal border (base) These areas had been found to be the most significant because the right second i c s often gave poor tracings except in patients having dilatation of the ascending aorta

The tracings were recorded during normal respiration Respiration was transcribed as an additional tracing by means of a bellows and a piezoelectric transducer with low frequency response

All measurements were made *during expiration* with the exception of the data of the second sound which were separately measured in both inspiration and expiration and they represent intervals from either onset of Q to onset of a sound or duration of a sound from onset to end *

Our tables present the measurements *obtained in the velocity tracing* with the use of *three different degrees of filtration* 0 to 100 Hertz† (Hz) 50 to 400 Hz and 400 to 800 Hz. These three bands had been found to contain all necessary clinical information by tests performed in clinical cases. In addition measurements were made in the *acceleration tracing* This was recorded with the band pass filter at 0 to 600 Hz the low pass, high limit being used in order to exclude noise Our filters have slopes of 48 db per octave. This slope which is sharper than that used by many others causes normal heart sound energy to be graphically confined to frequencies below 600 Hz With less sharp filter slope the energy would seem to reach higher frequencies.

The measurements included (1) duration of the I II III and IV sounds * (2) the electroacoustic interval Q-Ia* i.e., the interval between the onset of the ventricular complex of the ECG and the onset of the first large rapid vibration of the first heart sound (3) the intervals IV Ia Ia Ib, and Ia Ic dealing with the IV sound and various components of the I sound (4) the interval IIA IIP in expiration and inspiration (5) the interval IIA-os os being a small low frequency vibration that sometimes follows the P component of the second sound and grossly coincides with or closely follows the opening of the mitral valve and (6) the IIA III interval

All these measurements have clinical significance have been repeatedly studied in the past and may become altered in heart diseases.

Statistical analysis of the data was made and the following data were studied the mean the standard deviation (corrected for small samples) the standard error of the mean and the maximum and minimum values. All the minima and maxima were found to fall within the 98 per cent limits as defined by Student s t test.

When data concerning a given phenomenon were obtained on fewer than five subjects the data were omitted as being not statistically significant

Results

The results of the study are presented in Tables I II and III

Discussion

The duration of heart sounds was repeatedly investigated by Luisada and associates.[5,6] The first study was made with the Sanborn stethoscopic system and a similar study was subsequently made with a similar technique by Ongley and coworkers[7] In 1963 we repeated the study in ten normal subjects[8] with the use of a specially built calibrated system All these studies necessarily reflected the characteristics of the equipment employed Having a

In both cases, note should be taken [illegible] basic difference between the measurements in tracings with low frequency filtration and those with high frequency filtration. I the former the initial slow vibrations were considered as integral part of sound; thus, the duration of the sound was longer while the preceding intervals were shorter I high frequency tracings such slow vibrations were abolished by the filter This explains the shorter sounds and the longer intervals recorded with high degree of filtration.

†The term Hert is equivalent t the older term cycles per second.

*These designations are consistent with the recommendations of an International committee. Comparing these with other current symbols, I = S_1; II = S_2; III = S_3; IIA = A_2; IIP = P_2, and so on.

Table I *Data obtained at the apex (in milliseconds)*

	Duration of IV	IV-I	Q-I	Ia-Ib	Ia-Ic	Duration of I	IIA IIP (expiration)	Duration of II	IIA-oc	IIA III	Duration of III
Velocity 0-100 Hz											
Mean	65	96	55	32	63	122	29	58	75	111	71
S.D.	17	19	7	7	11	16	5	9	7	16	16
S.E.	4	3	2	1	2	3	1	3	2	[illegible]	4
Minimum value	40	60	45	25	50	95	20	40	65	120	45
Maximum value	90	130	70	40	90	160	40	60	90	160	90
Velocity 40-400 Hz											
Mean			58	30	58	103	23	47	70	112	61
S.D.			7	9	13	16	4	8	6	10	15
S.E.			1	2	3	3	1	2	1	4	9
Minimum value			50	20	45	75	20	35	65	120	40
Maximum value			75	55	90	130	35	65	85	140	90
Velocity 400-800 Hz											
Mean			58	19		44	16	23			
S.D.			10	6		14	7	11			
S.E.			2	1		3	2	2			
Minimum value			35	10		16	10	10			
Maximum value			85	33		65	30	50			
Acceleration											
Mean			59	26	53	74	23	38			
S.D.			10	8	8	21	6	8			
S.E.			2	1	2	5	1	2			
Minimum value			40	20	35	45	15	20			
Maximum value			80	40	70	140	35	55			

better phonocardiographic system such study deserved to be repeated

Intervals

Q-IA INTERVAL. This interval has special interest because it may become prolonged in clinical conditions. It was found to be longer over the base because of the lack of recording of some early sound vibrations. It was found to be longer in tracings recorded with high filtration for the same reason. Therefore, clinical comparison should be made only with our data, recorded either at the apex or at the midprecordium, and excluding the tracings at 400 to 800 Hz filtration. The average values were 55, 58, 59 msec. at the apex and 57, 57, 62 at the midprecordium. The maximum values were 70, 75 at the apex and 60, 75 at the midprecordium for velocity tracings; the maximum value for acceleration tracing was 80 at the apex and at the midprecordium.

Therefore, if one uses a velocity tracing, prolongation of the Q-Ia interval can be stated only *if the interval is longer than 75 msec.* This is somewhat longer than the usually accepted value.

IA IB INTERVAL. This interval measures the distance between the two main high frequency components of the first sound. It was found to be as long as 60 msec. (midprecordium, velocity 0 to 100 Hz) and as short as 10 msec. (apex, velocity 400 to 800 Hz). The averages were 32, 30 (apex) and 33, 27 (midprecordium), with shorter intervals for high filtration (19, 20) or acceleration tracings (26, 25).

IA IC INTERVAL. This interval measures the distance between the first and the third component of the first heart sound. Its prolongation should be considered as evidence that there is an ejection sound and therefore there is some cardiovascular abnormality. The average figures were 63, 58 (apex), 65, 56 (midprecordium), and 57, 52 (base) for velocity tracings, and 53, 2, 57 for acceleration tracings over the

Table II Data obtained at the midprecordium (in milliseconds)

	Duration of IV	IV Ia	Q-Ia	Ia-Ib	Ia-Ic	Duration of I	IIA IIP Expiration	IIA IIP Inspiration	Duration of II (expiration)	IIA-os	IIA-III	Duration of III
Velocity 0-100 Hz:												
Mean	[illegible]	81	57	33	63	115	29	46	51	73	103	72
S.D	18	13	10	8	11	16	6	5	9	7	11	13
S.E.	5	4	2	2	3	3	1	2	3	1	3	4
Minimum value	40	60	30	25	60	85	20	40	40	60	130	[illegible]
Maximum value	110	110	60	60	80	150	40	50	70	80	160	100
Velocity 50-400 Hz:												
Mean			57	[illegible]	56	97	[illegible]	45	50	70		
S.D.			8	5	9	13	5	10	9	7		
S.E.			2	1	2	3	1	4	2	1		
Minimum value			35	20	45	70	20	30	35	55		
Maximum value			75	40	75	120	40	55	65	80		
Velocity 400-800 Hz:												
Mean			[illegible]	20		35	23		25			
S.D			10	7		15	10		15			
S.E.			2	2		4	2		3			
Minimum value			60	10		10	10		10			
Maximum value			[illegible]	35		60	35		60			
Acceleration:												
Mean			62	23	53	73	26	41	42	[illegible]		
S.D			11	5	11	18	6	10	10	10		
S.E.			2	1	2	4	1	3	2	3		
Minimum value			25	15	35	35	15	30	25	55		
Maximum value			80	35	75	100	40	60	60	80		

three areas. The longest interval found was 90 msec for velocity tracings 50 to 100 Hz at the apex intervals of 80 msec. were not unusual with various filters and over the various areas. Thus an interval of 80 or 90 msec by itself cannot be considered as pathologic in a clinical case.

IIA IIP INTERVAL. This interval measures the distance between the aortic and pulmonary components of the second sound As longer intervals can be found in clinical cases the interest centers around the longest intervals that are found in inspiration and especially those measured at the base Over this area the average intervals were 47 43 44 45 The maximum intervals were 60 50 50 55 according to the type of filter and the type of tracing Thus an interval of 60 msec. in inspiration cannot be considered abnormal in a young adult.

IIA-OS INTERVAL. This interval has importance for evaluation of left atrial-left ventricular gradient of pressure. It can be measured only in some of the normal individuals and thus it acquires particular interest. The average data were 75 70 (apex) 73 70 69 (midprecordium) and 75 70 73 (base) The longest interval is of importance considering the occasional confusion between opening snap and third sound It was found to be 90 80 (apex) 80 80 80 (midprecordium) and 80 80 80 (base) Thus the *longest normal interval* is 90 msec and is still much shorter than the shortest II III interval (see below) It is still shorter than some intervals found in mild mitral stenosis or after mitral commissurotomy a fact that seems to point out the existence of additional elements that may prolong this interval in the above cases. The *shortest normal intervals* were found to be 65 65 (apex) 60 55 55 (mid

Table III Data obtained over second left interspace (base) (in milliseconds)

	Duration of IV	IV-I	Q-I	Ia-Ib	Ia-Ic	Duration of I	IIA-IIP		Duration of II (expiration)	IIA-os
							Expiration	Inspiration		
Velocity, 0-100 Hz										
Mean	62	88	61	30	57	100	25	47	54	73
S.D.	14	13	19	7	11	19	6	10	8	4
S.E.	5	5	2	1.5	3	4	1	4	2	1
Minimum value	40	71	50	20	40	75	20	35	40	70
Maximum value	80	100	80	40	75	130	40	60	70	80
Velocity, 50-400 Hz										
Mean			62	25	52	96	26	43	52	70
S.D.			8	5	9	17	4	8	6	8
S.E.			2	1	2	3	1	2	1	1
Minimum value			50	15	25	70	20	25	40	60
Maximum value			75	25	75	110	35	60	60	80
Velocity 400-800 Hz										
Mean			71	23		34	25	46	21	
S.D.			13	4		20	8	9	14	
S.E.			4	2		4	2	3	3	
Minimum value			43	20		10	19	29	15	
Maximum value			90	30		60	40	89	80	
Acceleration										
Mean			62	27	57	78	25	45	47	73
S.D.			14	7	14	21	6	9	8	4
S.E.			3	3	3	4	1	3	2	2
Minimum value			25	15	35	55	15	35	30	70
Maximum value			90	45	90	120	40	85	60	80

precordium) and 70 60 70 (base) Thus, one can occasionally encounter intervals as short as those found in mitral stenosis. This should indicate that the IIA-os interval alone is not sufficient for evaluation of left atrial-left ventricular gradient of pressure.

IIA-III INTERVAL. The interest of this interval is based on the need for recognition of a third sound The minimum value was 120 msec. and the maximum value of this interval was 160 msec. both at the apex. Thus a wide margin separates the minimum value of this interval from the maximum value of the IIA-os interval and excludes the possibility of misinterpretation.

One consideration should be made in regard to these intervals. When passing from no filtration or low filtration to high filtration, some low-pitched vibrations that are present at the beginning of each sound become smaller or disappear This causes a prolongation of all intervals. Therefore, comparison between our data and those of a given clinical case can be made only with a similar type of filtration Unfiltered acceleration tracings gave data which are similar to those of velocity tracings taken with medium filtration (50 to 400 Hz) On the other hand the high frequency vibrations of the first two components (a, b) of the first sound and those of the second sound (A, P) are closer when recorded with high frequency filtration.

Duration of sounds

DURATION OF I. Average duration is significant only in velocity tracings recorded at the apex or midprecordium with low filtration due to predominance of low frequency vibrations ending this sound in displacement tracings. It was found to be 122 msec. at the apex and 115 msec. at the

Table II Data obtained at the midprecordium (in milliseconds)

	Duration of IV	IV Ia	Q-Ia	Ia-Ib	Ia-Ie	Duration of I	IIA-IIP		Duration of II (expiration)	IIA-os	IIA-III	Duration of III
							Expiration	Inspiration				
Velocity 0-100 Hz												
Mean	65	81	57	33	65	115	29	46	54	73	[illegible]	72
S.D	18	13	10	8	11	16	6	5	9	7	11	15
S.E.	5	4	2	2		3	1	2	2	1	3	4
Minimum value	40	60	30	25	50	85	20	40	40	60	130	[illegible]
Maximum value	110	110	60	60	80	150	40	50	70	80	160	[illegible]
Velocity 50-400 Hz												
Mean			57	27	56	97	27	45	50	70		
S.D.			8	5	9	13	5	10	9	7		
S.E.			2	1	2	3	1	4	2	1		
Minimum value			35	20	45	70	20	30	35	55		
Maximum value			75	40	75	120	40	55	65	80		
Velocity 400-800 Hz												
Mean			71	20		35	20		23			
S.D			10	7		15	10		15			
S.E.			2	2		4	2		3			
Minimum value			60	10		10	10		10			
Maximum value			05	35		60	35		60			
Acceleration												
Mean			62	25	53	73	26	41	42	60		
S.D.			11	5	11	18	6	10	10	10		
S.E.			2	1	3	4	1	3	2	3		
Minimum value			25	15	35	35	15	30	25	55		
Maximum value			80	35	75	100	40	60	60	80		

three areas The longest interval found was 90 msec for velocity tracings 50 to 100 Hz at the apex *intervals of 80 msec. were not* unusual with various filters and over the various areas. Thus an interval of 80 or 90 msec by itself cannot be considered as pathologic in a clinical case

IIA IIP INTERVAL. This interval measures the distance between the aortic and pulmonary components of the second sound As longer intervals can be found in clinical cases the interest centers around the longest *intervals that are found in inspiration* and especially those measured at the base Over this area the average intervals were 47 43 44 45 The maximum intervals were 60 50 50 55 according to the type of filter and the type of tracing Thus an interval of 60 msec. in inspiration cannot be considered abnormal in a young adult.

IIA-OS INTERVAL. This interval has importance for evaluation of left atrial-left ventricular gradient of pressure. It can be *measured only in some of the* normal individuals and thus it acquires particular interest. The average data were 75 70 (apex) 73 70 69 (midprecordium) and 75 70 73 (base) The longest interval is of importance considering the occasional confusion between opening snap and third sound It was found to be 90 80 (apex) 80 80 80 (midprecordium) and 80 80 80 (base) Thus the *longest normal interval* is 90 msec and is still much shorter than the shortest II III interval (see below) It is still shorter than some intervals found in *mild mitral stenosis or after mitral com*missurotomy a fact that seems to point out the existence of additional elements *that may prolong this interval in the above* cases. The *shortest normal intervals* were found to be 65 65 (apex) 60 55 55 (mid

Experimental evidence in man of the electrocardiographic manifestations of papillary muscle dysfunction

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The electrocardiographic changes associated with papillary muscle dysfunction due to fibrosis, myopathy, and/or infarction of the left ventricle have been described previously.[1-4] Electrocardiographic changes associated with *acute* diseases of the papillary muscles consist of marked depression of Junction J usually associated with a slight convexity-upward deformity of the S-T interval (Fig. 1, *A*). The changes ordinarily seen in *subacute* disease of the papillary muscle consist of slight to moderate depression of Junction J usually associated with a slight convexity-upward deformity of the S-T interval and terminal inversion of the T wave. The electrocardiographic changes associated with *chronic*, fibrotic disease of the papillary muscle usually consist of moderate depression of Junction J and the S-T segment with a concavity-upward deformity of the S-T segment. The concavity-upward deformity of the S-T segment varies in extent from slight to marked (Fig. 1, *B*). U wave inversion and/or depression of the T-U segment are found in the electrocardiogram (ECG) of most patients with papillary muscle disease. Characteristically, the Q-T or Q-U interval is markedly prolonged. It should be emphasized that the above-described ECG changes of papillary muscle disease are part of a spectrum of change and may thus exhibit a great deal of overlapping.

Involvement of the left ventricular anterolateral papillary muscle by disease is suggested when the above changes are observed in Leads I, aV$_L$, V_5, and V_6, whereas changes in Leads II, III, aV$_F$, and V_1 through V_4 suggest involvement of the posteromedial papillary muscle. Excellent correlation has been found between these electrocardiographic changes and papillary muscle disease in postmortem specimens.[1-4]

Experimental evidence for the papillary muscle origin of the observed ECG changes in man has not been reported previously. However, a ready-made experiment, namely mitral valve surgery, affords an opportunity to observe in man the ECG changes due to papillary muscle injury. This is so because replacement of the mitral valve in man with a prosthetic device requires excision of the papillary

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midprecordium The longest sound was 160 msec at the apex (velocity 0 to 100 Hz) Thus only if a first sound lasts longer than 160 msec can one accept the fact that there is an early systolic murmur

DURATION OF III Usually this sound lasts from 70 to 80 msec However shorter sounds (40 to 50 msec) and longer sounds (100 msec) were observed In order to state that there is a pathologic middiastolic murmur one should observe a series of vibrations that is longer than 100 msec.

DURATION OF IV AND DURATION OF II The duration of the fourth sound has less significance for clinical comparison and can be found in the tables The duration of the second sound obviously depends on the width of the A P interval However it should be mentioned that the longest second sound was 70 msec (base inspiration velocity 0 to 100 Hz) Thus any longer sound would represent the beginning of an early diastolic murmur

Summary

The duration of the heart sounds the Q-I interval and the intervals between sounds as well as between their components were studied in 23 normal subjects The study was made with new calibrated equipment which records displacement velocity and acceleration tracings, and which contains provisions for the application of different filters.

The data obtained will serve for evaluation of those found in clinical cases.

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Experimental evidence in man of the electrocardiographic manifestations of papillary muscle dysfunction

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The electrocardiographic changes associated with papillary muscle dysfunction due to fibrosis, myopathy, and/or infarction of the left ventricle have been described previously.[1-4] Electrocardiographic changes associated with *acute* diseases of the papillary muscles consist of marked depression of Junction J usually associated with a slight convexity-upward deformity of the S-T interval (Fig. 1, *A*). The changes ordinarily seen in *subacute* disease of the papillary muscle consist of slight to moderate depression of Junction J usually associated with a slight convexity-upward deformity of the S-T interval and terminal inversion of the T wave. The electrocardiographic changes associated with *chronic* fibrotic disease of the papillary muscle usually consist of moderate depression of Junction J and the S-T segment with a concavity-upward deformity of the S-T segment. The concavity upward deformity of the S-T segment varies in extent from slight to marked (Fig. 1, *B*). U wave inversion and/or depression of the T-U segment are found in the electrocardiogram (ECG) of most patients with papillary muscle disease. Characteristically, the Q-T or Q-U interval is markedly prolonged. It should be emphasized that the above-described ECG changes of papillary muscle disease are part of a spectrum of change and may thus exhibit a great deal of overlapping.

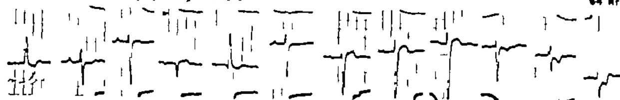
Involvement of the left ventricular anterolateral papillary muscle by disease is suggested when the above changes are observed in Leads I, aVL, V_5, and V_6, whereas changes in Leads II, III, aVF, and V_1 through V suggest involvement of the posteromedial papillary muscle. Excellent correlation has been found between these electrocardiographic changes and papillary muscle disease in postmortem specimens.[1-4]

Experimental evidence for the papillary muscle origin of the observed ECG changes in man has not been reported previously. However, a "ready-made" experiment, namely mitral valve surgery, affords an opportunity to observe in man the ECG changes due to papillary muscle injury. This is so because replacement of the mitral valve in man with a prosthetic device requires excision of the papillary

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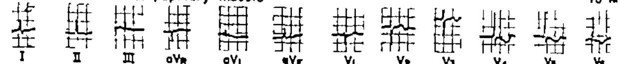
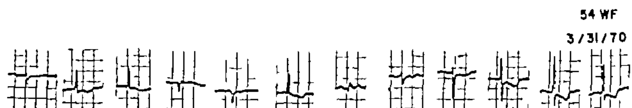


Fig. 1 *A* ECG recorded from a 61 year-old woman just prior to death showing changes characteristic of acute papillary muscle disease Examination of the heart at necropsy showed acute infarction of the left ventricular anterolateral papillary muscle. *B* ECG recorded from a 70-year-old woman showing changes characteristic of chronic papillary muscle disease. At necropsy the left ventricular anterolateral papillary muscle showed diffuse scarring and fibrosis.



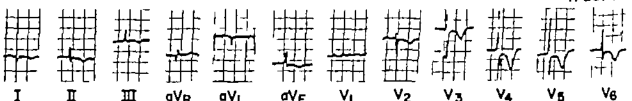


Fig 2 Pre and postoperative ECG s of a 54-year-old woman who had the mitral valve replaced and papillary muscles excised The postoperative tracing shows changes characteristically found in acute papillary muscle disease

muscles at their bases leaving a raw injured endocardial surface in these areas. Thus the ECG changes of papillary muscle injury would be expected if the previously presented hypothesis[1-4] concerning their origin is correct. Therefore we reviewed clinical records of patients before and after replacement of the mitral valve to learn whether or not ECG changes characteristic of papillary muscle disease followed The ECG s of patients who had an open mitral commissurotomy while on cardiopulmonary bypass were examined as controls since in those patients the papillary muscles were not excised or damaged except possibly for minor damage secondary to manipulations.

Clinical material

The clinical records of adult patients hospitalized at Charity Hospital of Louisiana at New Orleans on the Tulane University Medical Service who underwent mitral valve replacement or mitral commissurotomy with the use of total cardiopulmonary bypass in both were randomly examined for pre- and postoperative configurations of the ECG s. Since the ECG changes indic

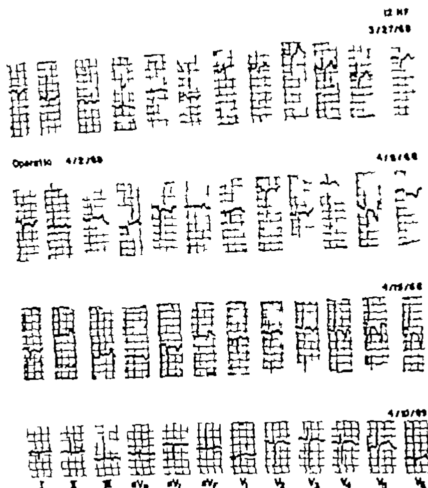


Fig. 3 Pre- and postoperative ECG' recorded from a 12-year-old girl who had the mitral valve and papillary muscles excised and a prosthetic valve inserted. The early postoperative tracings (April 8, 1968 and April 15 1968) show changes characteristic of those found in acute disease of the papillary muscles. A later tracing (April 10, 1969) shows return t the preoperative configuration, pparently representative of healing of the injured myocardial area.

ative of papillary muscle disease are reflected best in the precordial leads, a large number of early postoperative ECG s were not available for study because the surgical dressings on the chest in most instances permitted only Leads I II III aV_R, aV_L, and aV to be recorded immediately postoperatively Thus, no effort was made to determine the incidence of ECG changes of papillary muscle injury

Most patients were receiving digitalis preparations and a diuretic prior to operation, but drugs were usually discontinued one or two days preoperatively Operations for both mitral valve replacement and mitral commissurotomy were performed with the use of total cardiopulmonary bypass without coronary artery perfusion

Pump times" for mitral valve replacement (35 to 45 minutes) were slightly longer than for commissurotomy (20 to 35 minutes)

Results

Mitral valve replacement. Six patients whose ECG series were suitable for study had ECG s with patterns typical of papillary muscle injury following excision and replacement of the mitral valve. Fig 2 shows an ECG of a patient who developed classical changes of acute papillary muscle injury following operation Fig 3 illustrates

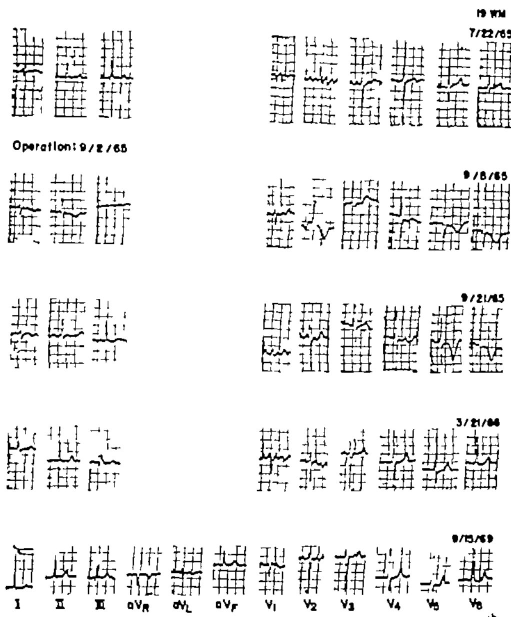


Fig 4 Pre- and postoperative ECG s recorded from a 19 year-old man who had mitral valve replacement with excision of the papillary muscles. The early postoperative tracings (Sept. 8 1965 and Sept 21 1965) show changes previously attributed to CNS damage as well as changes characteristically found in acute papillary muscle disease. Later tracings (March 21 1966 and Sept. 15 1969) show a return of the ECG to a preoperative configuration, compatible with healing

tracings from another patient with ECG changes of acute papillary muscle injury following operation and also changes associated with healing The ECG of another patient (Fig 4) illustrates not only papillary muscle injury but also changes described previously for injury to the central nervous system (CNS)[5] CNS disturbances are well known to occur during open heart surgery in which total cardiopulmonary bypass is used[6,7] The ECG s which showed changes postoperatively always suggested involvement of the left ventricular anterolateral papillary muscles whereas changes associated with posteromedial papillary infarction were rarely seen

Open mitral commissurotomy No ECG s showed typical changes of papillary muscle infarction in patients who merely had open mitral commissurotomy Six patients had ECG s suitable for study recorded early in the postoperative period Only minor changes in an occasional ECG occurred (Fig 5) which apparently re-

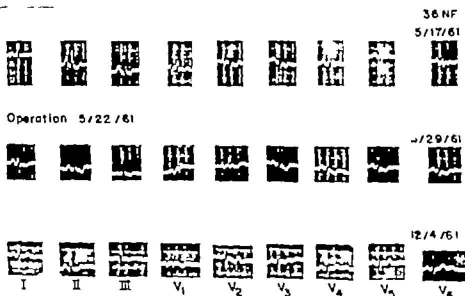


Fig. 5 Pre- and postoperative ECG's recorded from 36-year-old woman who had an open mitral commissurotomy. The T waves are inverted in the early postoperative ECG (May 29 1961) but the changes in Junction J and S-T segment are minor and not characteristic of acute papillary muscle disease. These tracings show the greatest changes encountered in the six patients who had open mitral commissurotomy

sulted from manipulations of the papillary muscles during the operation. The muscles were not excised

Discussion

ECG's following mitral valve replacement at which time the papillary muscles were excised leaving a raw injured endocardial surface showed changes typical of those described previously for acute papillary muscle injury.[4] These characteristic patterns were not present in any of the preoperative tracings. ECG's recorded from patients after open mitral commissurotomy in which the papillary muscles were not excised did not show such changes. These findings support the concept that injured papillary muscles produce typical ECG changes previously described for papillary muscle disease.[4] The mechanism responsible for the S-T segment shift is essentially as described for currents of injury. The role of electrolyte shifts during cardiopulmonary bypass, from drug therapy or anesthetic agents, and the like that might be considered to produce these ECG changes was excluded since these factors were essentially the same for both types of open mitral valve surgery

The patients with papillary muscle excision whose early postoperative ECG's included the precordial leads always had changes of papillary muscle injury. Since it is likely that some papillary muscle damage occurs even during commissurotomy, occasional slight ECG changes of papillary muscle injury should be expected after such procedures. In fact, this may explain some of the minor changes observed in such patients during this study (Fig. 5). These tracings also reveal the extreme sensitivity of the ECG in detecting even slight injury to the papillary muscles.

The papillary muscles are subendocardial structures which may be subjected to large amounts of stress. In addition the arterial blood supply is tenuous.[5] Thus, it is not surprising that the papillary muscles are often the site of myocardial damage especially with cardiomyopathy, myocarditis and coronary artery disease. The precise mechanism by which papillary muscle injury produces ECG changes is not completely known. However, the changes observed in this study can be readily explained with the use of present concepts of currents of injury.[6] The downward shift of Junction J is likely due to a

current of injury effect located at the raw surface where the papillary muscle was excised thus leaving an injured surface underlying the exploring electrode This resting current of injury resulting from the raw injured surfaces left at the area of the basal attachments of the papillary muscles to the left ventricular endocardial surface would tend to shift the ECG base line upward However because of compensating balancing forces in the ECG a downward shift of Junction J results [8]

Since both the medial and lateral papillary muscles are injured during replacement of the mitral valve with an artificial prosthesis one might have expected to see ECG changes of papillary muscle injury in all precordial leads Yet the changes recorded were of anterolateral papillary muscle injury alone One possible explanation for this observation is that the manifested electrical forces originating from the anterolateral papillary muscle group are relatively stronger than and thereby negate the electrical forces originating from the posteromedial group Also since the exploring electrodes (V_5 and V_6) are much closer and perpendicularly oriented to the anterolateral papillary muscle than those overlying the posteromedial muscles (V_1 through V_4) the manifested injury current forces are more effectively oriented for recording by V_5 and V_6 than by V_1 through V_4 The precordial leads are semidirect and would therefore reflect larger deflections than the standard leads. Finally thoracotomy and cardiac manipulations alter the spatial anatomic orientation of the heart within the thorax with respect to electrode placements on the anterior chest wall Thus could explain why changes produced by injury to the posteromedial papillary muscles were less evident in the postoperative recordings than in patients who have nonsurgical injury to these muscles such as with myocardial infarction

Summary

ECG changes previously ascribed to disease of the anterolateral papillary muscles were seen in the six patients who had excision of the papillary muscle with replacement of the mitral valve whereas no patients who had open commissurotomy without injury to or removal of the papillary muscles had such changes. These findings support the concept that electric forces originating in the injured papillary muscle cause ECG changes previously described for papillary muscle disease and dysfunction

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Experimental and laboratory reports

The production of congenital heart defects with the use of antisera to rat kidney, placenta, heart, and lung homogenates

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Antibodies may affect fetal growth and development. This has been shown in amphibians by adding antisera to the developmental medium in the chick by injections in ovo and in mammals by injections in vivo (see Brent and Barrow[1] for reviews)

Brent and his colleagues[2-4] and David and Mercier Parot[5-8] have reported that antisera made in rabbits to whole rat kidney homogenates produced a spectrum of gross congenital malformations in fetuses of pregnant rats given the antiserum The type of malformations produced depended on the time of administration but generally followed the pattern previously reported for trypan blue [9-12] i.e. when given on the ninth or tenth day of gestation central nervous system anomalies occur if given on the ninth to eleventh day heart anomalies result and when given after the eleventh day only urogenital defects or no anomalies are observed. Because of the similarity of action of the antisera and trypan blue and because these agents are thought not to cross the yolk sac placenta in the rat [13] it has been hypothesized that their mechanism of action lies in disrupting the function of the yolk sac placenta a membrane known to be very active in transport early in gestation in the rat (from implantation on the eighth day to about the twelfth or thirteenth day) The fact that antibodies to basement membrane of kidney placenta, and yolk sac all cross-react with each others antigens supports this view and provides a plausible explanation for the antisera s action. Although a high incidence of heart defects has been described after administration of trypan blue [9-12] neither Brent and colleagues [2-4] nor David and Mercier Parot[5-8] reported comparable incidences for cardiac defects secondary to kidney or placenta antisera. They did not, however do microdissections of the heart. Barrow and Taylor[14] have recently described a rapid and accurate method for evaluating congenital heart defects in rats. The present study was undertaken (1) to determine the incidence of congenital heart malformation in the fetuses of pregnant rats given antisera to kidney placenta, lung, and heart and (2) to describe the types of heart defects produced.

Methods

Kidney lung heart, and chorioallantoic placenta tissues were removed from Long

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Table I. Summary of control data

Total litters	111
Total implants	1 203
Mean number of fetuses per litter	10 8
Total resorptions (I)*	79
Per cent of resorption (I)	6 6
Total resorptions (II)†	53
Per cent of resorptions (II)	4 6
Total number of fetuses	1 124
Total normal fetuses	1 095
Mean weight of normal fetuses	3 94 ± 0 47‡
Total malformed fetuses	29
Total malformed per total number of fetuses (in per cent)	2 6
Mean weight of malformed fetuses	3 91 ± 0 40
Number of fetuses with cardiac malformations	1§

*Including whole litter resorptions.
†Excludes litter in which all fetuses were resorbed.
‡±S.D.
§A interventricular septal defect.

Evans rats (Research animals Braddock Pa.) and homogenized and lyophilized whole kidneys from other Long Evans rats were used to prepare renal basement membrane as described by Spiro.[15] Three young New Zealand white rabbits (Holsenbeck Rabbitry, Glen St. Mary, Fla.) for each antigen were immunized with 50 mg of material for the homogenates and 25 mg for the basement membrane in 2 ml of saline mixed with 2 ml of Freund's complete adjuvant at weekly intervals for five to six weeks and then monthly. Beginning with the sixth week 50 ml were bled from the ear and the serum was spun and frozen at −40° C. After approximately 250 ml of serum had been obtained for each antigen each antiserum was pooled and stored. Pregnant Long Evans rats (the first day on which sperm were found in the vagina was considered to be day 1) were injected on the ninth gestational day with either heart, lung, kidney, placenta or renal basement membrane antiserum in doses ranging from 1 to 3 ml per 100 Gm of pregnant rat. On the twenty first day of gestation the animals were killed and their fetuses were removed, counted, examined and weighed and fixed in Bouin's solution to be later microdissected as previously described.[14] Control animals were also injected on the ninth day with either saline, normal rabbit serum, anti-bovine-serum albumin or human gamma globulin in doses up to 3 ml per 100 Gm and these were handled identically to the treated group.

Results

Studies utilizing control animals (1,124 fetuses) of the Long Evans strain indicated the malformation rate and resorption rate to be 2 6 and 6 6 per cent respectively with control fetuses having a mean weight of 3 94 ± 0 47 grams (Table I). The details regarding the experimental groups are given in Table II. Kidney antiserum at doses of 1 ml per 100 Gm of mother's weight on day 9 resulted in three prominent effects. (1) Fetal death in utero (resorption rate) was increased (59 per cent vs. 7 per cent for controls). Higher doses using this antiserum such as 1 5 or 2 ml per 100 Gm produced 100 per cent resorption rates. (2) Severe weight reduction of the fetuses was a common feature. Even the nonmalformed fetuses showed significant reductions in weight although these were not as marked as those of the malformed animals. Virtually all the weights shown in Table II are significantly less than the control value of 3 94 ± 0 47 ($p < 0.05$). (3) A highly significant incidence of congenital malformations—with a large proportion of these being cardiac malformations—were noted (77 per cent). Placental antiserum in equivalent doses on the ninth gestational day produced a remarkably similar pattern to the kidney antisera. Notably both of these began losing a considerable amount of teratogenic activity by the eleventh day. Purified renal basement membrane antiserum was also teratogenic but less so than whole kidney homogenate antiserum. The reasons for this are not entirely clear. Smaller doses of antigen were used but the preparations were purified basement membrane material and this should not have been a factor. Lung antiserum was also teratogenic but less so than kidney or placenta and a larger dose (threefold) was required to demonstrate important teratogenic effects. Under the conditions of this experiment heart antiserum even at large doses showed no teratogenic effect nor did it cause alterations in the resorption rate.

The cardiac malformations were nonspecific but generally were characterized by

Table II Cardiovascular malformations after administration of antisera to kidney, placenta, lung, and heart

Antisera	Day	No. litters and (fetuses)	Resorption rate (%)	Normal		Mean weight	Malformed		Mean weight	Malformed with cardiac malformation	
				No.	Per cent		No.	Per cent		No.	Per cent
Kidney (1 ml. per 100 Gm.)	9	11(46)	59	11	24	2.66 ± 0.26	35	76	3.22 ± 0.63	27	77
	11	5(39)	29	26	67	2.94 ± 0.44	13	33	3.70 ± 0.61	4	30
Renal basement membrane (3 ml. per 100 Gm.)	9	4(31)	23	11	35	3.23 ± 0.38	20	65	3.18 ± 0.48	4	20
Placenta (1 ml. per 100 Gm.)	9	7(30)	64	6	20	3.32 ± 0.70	24	80	2.98 ± 0.72	16	67
	11	4(28)	35	20	71	3.27 ± 0.87	8	29	2.76 ± 0.39	2	25
Lung (3 ml. per 100 Gm.)	9	3(36)	40	20	54	3.49 ± 0.40	16	46	2.71 ± 0.62	3	8
	11	4(36)	5	26	72	3.35 ± 0.33	10	28	3.22 ± 0.32	0	0
Heart (3 ml. per 100 Gm.)	9	3(32)	9	30	94	3.41 ± 0.47	2	6	3.20 ± 0.00	0	0
	10	3(33)	0	27	82	3.57 ± 0.38	6	18	3.34 ± 0.60	0	0

*Dose of 5 ml. per 100 Gm. produced 100 per cent resorptions.

Table III Cardiac malformations produced by antisera

Malformation	Antiserum					
	Kidney 1 ml./100 Gm., day 9	Kidney 1 ml./100 Gm., day 11	Placenta, 1 ml./100 Gm., day 9	Placenta 1 ml./100 Gm. day 11	Lung, 3 ml./100 Gm., day 9	Renal basement membrane 3 ml./100 Gm. day 9
Situs inversus	1	—	1	—	—	—
Situs with truncus	2	—	2	—	—	—
Single ventricle	1	—	1	—	—	—
Truncus arteriosus	1	1	4	—	—	2
Transposition	4	—	1	—	2	—
Interventricular septal defect	3	1	1	—	1	—
Overriding aorta	—	—	—	—	—	
Atrial shifts	3	—	3	—	—	2
Abnormal aortic outflow	9	2	2	1	—	—
Abnormal pulm. outflow	2	—	2	1	—	—
Abnormal great vessels	2	—	1	—	—	—

rotation and displacement of ventricles and at times the atria, and great vessel abnormalities (Table III). These were similar to those described for trypan blue administered on the ninth day of gestation but important differences will be discussed below. Complete situs inversus with and without truncus arteriosus occurred on six occa-

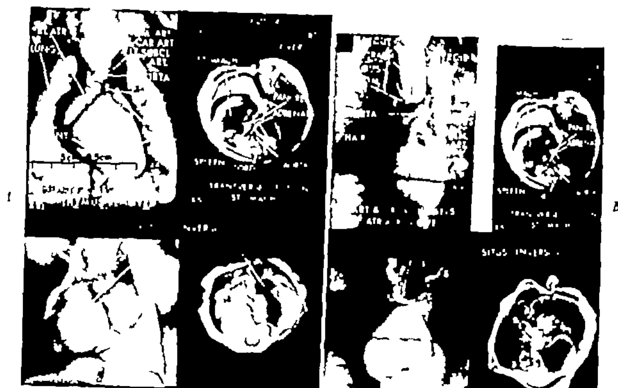


Fig. 1 Rat kidney antiserum 1 ml. per 100 Gm given on the ninth day of gestation 2 littermates are shown. Above are normals for comparison. 1 Complete situs inversus is present. The heart anatomically was otherwise normal. *B* Situs *inversus with truncus arteriosus.*

sions (Figs. 1 and 2) Truncus arteriosus and transposition of the great vessels were seen with about equal frequency and were the most common severe cardiac defect seen (Fig 3) Interventricular septal defects atrial shifts abnormal aortic and *pulmonary outflow* and abnormal great vessels were noted frequently (Figs 4 to 6) and single ventricle and associated defects also were seen (Fig 7) It should be pointed out that patent ductus arteriosus will not be found in these experiments since the animals are put to death before term in addition when the methods described here are used[14] atrial septal defects are not appreciated

Discussion

These results confirm and considerably extend *previous studies.*[1,4-9] *Antisera* to kidney and placenta are known to be potent teratogens which produce a variety of defects when given on *the ninth* gestational day and the teratogenicity is rapidly decreasing by the eleventh day In contrast to previous reports, the present study *indicates* that cardiovascular defects occurred with a significant incidence—77 per cent for antikidney serum and 67 per cent for placenta when given on day 9 Lung and purified renal glomerular basement membrane antisera were also teratogenic but were *not so potent as kidney and placenta.*

The wide spectrum of defects reported in these experiments is somewhat similar to those seen after trypan blue administration on days 9 10 or 11 (although there are important differences) [9,13] Since both these agents act early in gestation with a rapid falling off in teratogenicity on day 11 since the central nervous system defects and cardiovascular defects are somewhat similar *since there is no suggestion of specificity* in any type of defect, and since neither teratogenic antiserum nor trypan blue has *been shown to cross the yolk sac placenta* and concentrate in the embryo but does localize in the yolk sac, it seems likely that *the mechanisms mediating the defects are* similar If this is so one would expect subteratogenic doses of antisera to kidney and *trypan blue given in combination to be* significantly teratogenic. This indeed proves to be the case.[14] However this still does not *provide an adequate explanation for the* mechanism of action of either of these agents.

Essentially there are three p ... *ex*



Fig. 2. Rat placental antiserum, 1 ml. per 100 Gm., given on the ninth day of gestation. *A*, Situs inversus. *B*, In the same fetus microdissection is shown with comparable normal sections above.

planations for the action of teratogenic antisera. The first possibility is that these agents affect the mother. Kidney, placenta, and lung antisera all produce glomerulonephritis with the development of proteinemia and azotemia when injected into rats.[17] However, the nephrotoxicity is usually gradual in onset and progressive. It is difficult to conceive that the pregnant rat would develop severe azotemia within 24 to 48 hours after injection, the time period during which the antisera must act when injected on day 9, since the period of organogenesis is over after day 12 (for the nervous and cardiovascular systems). Wilson[4] also showed that neither marked liver damage secondary to carbon tetrachloride (CCl_4) nor severe anemia resulted in malformations, although the pregnant animal

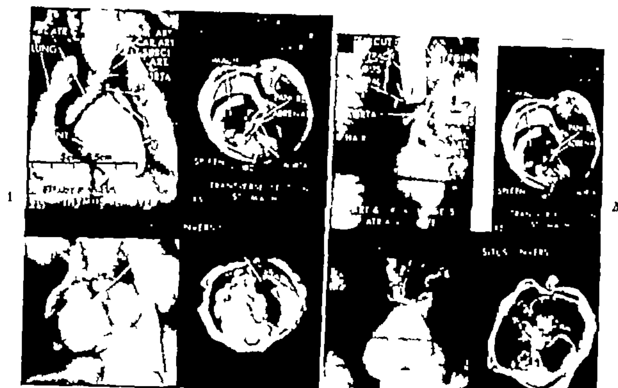


Fig. 1 Rat kidney ant serum 1 ml per 100 Gm. given on the ninth day of gestation 2 littermates are shown. Above are normals for comparison *A* Complete situs inversus is present. The heart anatomically was otherwise normal. *B* Situs inversus with truncus arteriosus.

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Essentially there are three p d ex



Fig. 2. Rat placental antiserum, 1 ml. per 100 Gm., given on the sixth day of gestation. *A*, Situs inversus. *B*, In the same fetus, microdissection is shown with comparable normal sections above.

planations for the action of teratogenic antisera. The first possibility is that these agents affect the mother. Kidney, placenta, and lung antisera all produce glomerulonephritis with the development of proteinemia and azotemia when injected into rats.[13] However, the nephrotoxicity is usually gradual in onset and progressive. It is difficult to conceive that the pregnant rat would develop severe azotemia within 24 to 48 hours after injection, the time period during which the antisera must act when injected on day 9, since the period of organogenesis is over after day 12 (for the nervous and cardiovascular systems). Wilson[11] also showed that neither marked liver damage secondary to carbon tetrachloride (CCl_4) nor severe anemia resulted in malformations, although the pregnant animals were toxic. A second possibility is that the



Fig 3 Rat kidney antiserum, 1 ml. per 100 Gm. given on the eleventh day of gestation. Normal specimens are shown above



Fig 4 Antiserum to adult kidney 1 ml. per 100 Gm., given on the ninth day of gestation. A normal is shown on the left (From Barrow and Taylor A rapid method for detecting malformation in rat fetuses, J Morph 127:291 1969 published by The Wistar Institute Press.)



Fig 5 Antiplacental serum, 1 ml. per 100 Gm. given on the eleventh day of gestation. Comparable normal is shown at left.

antiserum reaches the fetus and directly affects it thereby producing malformations. However since the antibodies fail to concentrate in the embryo[11] since there is no specificity of defects—i e since kidney antiserum does not produce kidney abnormalities and heart antiserum does not produce heart malformations[2]—and since adult heart antiserum in fact shows little if any teratogenicity this alternative seems unlikely Nephrotoxic antisera have not been tested for teratogenicity in chick eggs after injection in ovo a technique which would provide a method for direct injections, so the second option remains an open question The third possibility which might explain the teratogenicity of these agents is that yolk sac transfer is adversely affected in some way The yolk sac placenta (or endoderm or membrane) is the major pathway for embryonic nutrition until the twelfth to thirteenth day when the chorioallantoic placenta begins its transfer function The fact that the yolk sac layer contains basement membrane which reacts with antisera to basement membrane of kidney chorioallantoic placenta lung and yolk sac and that teratogenic antisera concentrate in this layer[4] and not in the embryo is the mo[illegible] g argument for the antisera s mode of action in the pregnant rat and is the one presently espoused [1-4]

If these facts are true one would expect purified glomerular renal basement membrane antiserum to be teratogenic. This antiserum was in fact quite teratogenic, although higher antiserum doses were required The reasons for this, as mentioned above are unclear Possibilities include a loss of the basement membranes during preparation a less potent antibody response with the antigen in purified form or poor antibody producers in one or two of the three rabbits used The less potent basement membrane antiserum is still quite teratogenic and this is the significant point

While the specific mechanism whereby the cardiovascular and other defects were produced in this experiment remains unknown the defects nevertheless offer an interesting opportunity to stu[illegible] mc



Fig. 6 Antikidney serum, 1 ml. per 100 Gm., given on day 9 Normals are shown above for comparison.



Fig. 7 Single ventricle defects and associated anomalies. *A* Produced by antiplacental serum, 1 ml. per 100 Gm. on day 9 *B* Produced by antikidney serum, 1 ml. per 100 Gm., on day 9

malformations. As seen in Table III these tend to be severe and encompass a wide variety of cardiac malformations. Although structural abnormalities of the heart such as single ventricle and interventricular septal defects were observed the common abnormalities involved the outflow tracts and proximal great vessels. Truncus arteriosus and transposition, both as isolated defects and seen in conjunction with situs inversus (which occurred in six instances) were common as were aortic outflow tract abnormalities such as high aortic valve and overriding aorta. These complexes are

among the most common human cardiovascular malformations.

It is pertinent that teratogenic antisera used in this experiment resulted in both truncus abnormalities and transposition complexes whereas trypan blue produces predominantly transposition complexes. These findings would suggest that perhaps trypan blue and antisera act in a different fashion after all

Summary

Pregnant Long Evans rats received antisera to adult rat kidney lung and heart rat placenta and purified glomerular basement membrane on the ninth to eleventh days of gestation in doses ranging from 1 to 3 ml per 100 Gm The teratogenic antisera produced increased resorption rates, reductions in fetal weight and significant malformations—with the exception of heart antiserum which was not teratogenic in this experiment Kidney and placenta antisera had a malformation rate of 76 and 80 per cent with nearly three fourths of these being cardiovascular defects. Glomerular basement membrane and lung antisera were also teratogenic but less so The cardiovascular malformations included situs inversus associated with truncus (4) as well as single ventricle (2) truncus arteriosus (8) various transpositions (7) interventricular septal defects (6) and several aortic outflow tract or proximal aorta abnormalities. These abnormalities were compared to those produced by trypan blue which produces mostly transposition complexes as well as to those produced by other teratogenic agents. The results suggest that antiserum produces its own unique spectrum of malformations, somewhat different from those produced by trypan blue and therefore that the two agents may have different modes of action

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Recovery of the moving dipole from surface potential recordings

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During the past decade the search for physiologically meaningful representations of the cardiac generator from surface electrocardiograms (ECG's) has intensified.[1] Despite inadequacies of recording and display, the vectorial interpretation of the ECG and the direct vectorcardiogram remain the major "inverse solutions" in clinical practice. Unfortunately, these representations leave unanswered the problem of origin. Where in the heart is the abnormal vector generated? There are times when an exaggerated anterior vector represents an addition to the activation front anteriorly (as in right ventricular hypertrophy) but other times may result from reduction in a posteriorly directed wavefront (as in posterior infarction). Timing of such vectors frequently does not separate such origins; thus, locus becomes highly pertinent.

Of other equivalent generators besides the fixed-location variable moment dipole of the vectorcardiogram, the multiple fixed moment dipole model and the principal factor models are interesting but too cumbersome for extended biomedical use.[2,3] The most appealing to us is the equivalent dipole with variable location and moment.[4] This would especially obtain if the deficiencies of the single dipole during obvious instants of high cardiac multipolar activity could be compensated for by utilizing a two-dipolar model.[9] Classical integration of potential over the body surface to obtain the equivalent dipole requires many electrode sites for such reduction. Weiss and Fischmann[10] estimated errors of 15 per cent for 100 electrodes as compared with the results obtained from 150 electrodes when utilizing surface integration for calculating the equivalent dipole. The solution of simultaneous lead vector equations should permit determination of dipole moment and locus from far fewer electrode sites. A ready approach to such computation has been described by Helm and Chou.[11] This study compares the success of recovery of a moving dipole in a homogeneous spherical model according to the number of surface electrodes employed and the relative amount of noise permitted. The method of

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computation is a search procedure for a site where the solution of simultaneous lead vector equations for the dipole moment yields the least error of fit to the known surface voltages

Methods

A sphere 10 units in radius was divided into 140 sections of equal area so that the centroids of each area element were designated by a matrix of 7 × 20 The 7 rows represented levels of latitude and the 20 columns fell on lines of longitude Two current dipole series one designated L and the other R of 8 instants each were utilized both singly and in combination to compute resulting voltages at the 140 sites on the sphere The Wilson Bayley[12] equation was used to calculate both the potential on the spherical boundary for the eccentric dipole series and the lead vectors used later in the recovery process The Gabor Nelson[8] equations were employed to obtain the equivalent dipole resulting from the simultaneous effect of the two dipoles

Noise was simulated by introducing at each electrode site an element of voltage derived from a random number table[13] The magnitude of the noise for a whole set (i.e voltages from 140 electrode sites at 8 instants in time) was set so that the mean absolute noise level was 5 per cent or 1 per cent of the mean absolute signal level

Recovery of each dipole series was computed by a search program which sought the dipole locus which produced the least error i e discrepancy between the given surface voltage and that computed for the test dipole The test dipole moment was determined by simultaneous solution of the lead vector equations relating the internal test site to the external electrode sites (see appendix for details) The number of electrodes was reduced from 28 to 20 and finally to 7 The sets of 28 and 7 were chosen because of the obvious advantage to magnetic tape applications for which 7 channel recording is standard Unlike the evenly distributed sets of 20 the distribution was concentrated over the precordial zone of high signal amplitude instead of evenly over the sphere

The computations were done on a PDP 9 laboratory computer with a 16K memory For a final set of comparisons employing voltages analogous to that resulting from a more dispersed generator than the single or double dipole we transferred to the sphere data recorded from the human chest during the inscription of the QRS complex The human data were digitized from 7 channel FM analog tape recordings from a normal 23 year-old man. Noise had been reduced by the averaging of 50 successive beats at each electrode site and time alignment to within 0 15 msec. had been secured by triggering from the differentiated control lead recorded on the eighth or voice tract

For all sets the error of recovery for each instant was estimated by subtracting the coordinates of the new locus vector and the new moment vector from the original (input) locus and moment vectors. This in turn gave the coordinates of the error vectors. For each complete series the estimate of error was taken as the square root of the sum of the squares of error vectors divided by the sum of the squares of input vectors. When the input vector was not known the result of the Gabor Nelson integration was accepted as reference for the estimate

Results

Fig 1 illustrates the effect of noise on dipole recovery it contains a series of eight known dipoles (black lines) and the estimates of locus and moment based on the voltages produced on the spherical boundary The estimate by integration with the Gabor Nelson equations is virtually superimposed upon the original input and is therefore not separately seen The dashed lines represent approximation of the equivalent dipole by the Helm Chou[11] (lead vector) equations when *no* noise was introduced and voltages from 28 surface electrodes were employed The periodically broken lines (1 per cent noise) and dotted lines (5 per cent noise) show increasing departures in the reapproximation with increasing levels of noise. Note that noise introduced greater error in the estimates when the signals were relatively low as at the beginning and end of the series. This was truer of locus than moment moment vectors can be seen to remain parallel (i e equal in orientation)

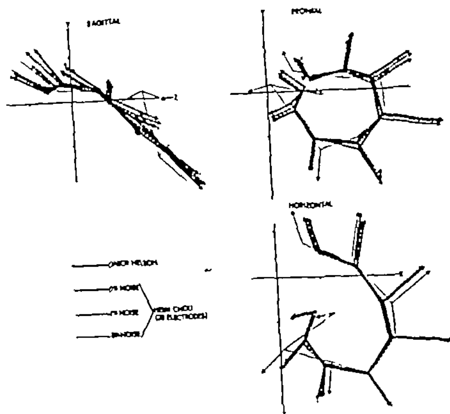


Fig. 1 Effect of noise on dipole recovery

and of similar magnitude despite displacement of their origins. As noted in Table I reducing the number of electrodes used in the recovery process for the single dipole resulted in only slight deterioration of the approximations.

Fig 2 shows the effect of electrode number on attempted solution for the equivalent dipole when two dipoles were used as the original input inside the sphere. Not having a single input dipole for comparison we employed the Gabor Nelson results as a reference for the six instants under examination (black lines) Approximation was relatively poorer with only 7 electrodes (18 per cent for moment and 43 per cent for locus as indicated in Table I) but there was progressive improvement with 20 and 28 electrodes.

Finally a similar set of attempts was made to approximate the equivalent dipole from voltage sets obtained from the voltage maps of human subjects. The Gabor Nelson estimates of locus and moment for the equivalent dipole were used as reference and formed smooth loops. However the locus approximations by the lead vector method were so erratic as to make an overlay of loops unintelligible to inspection We, therefore, have shown in Fig 3 the result of estimates with 7 20 and 28 electrodes by the Helm-Chou equations by representing locus and moment in terms of scalar lead components. The estimates at 5 msec. intervals are shown scattered widely off the locus curves but missing the moment curves by a greatly reduced margin The over all estimates of discrepancy between the Gabor \elson approximations and the Helm-Chou approximations are also summarized n Table I

Discussion

In order to cope with the problem of a heart source more complex than a single instantaneous dipole, we have employed as standard the equivalent dipole obtained by summating over all 140 surface points

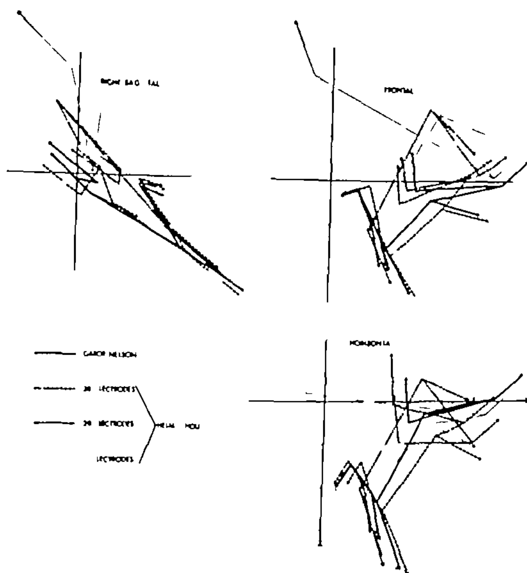


Fig 2 Effect of electrode number on attempted solution for the equivalent dipole when two dipoles were used as the original input inside the sphere

of the surrounding sphere Our own observations have indicated that detectable deterioration of this approximation occurs with electrodes fewer than 250 and Weiss and Fischmann[18] have indicated that serious error arises below 100 electrodes Because 140 is a useful minimum number of electrodes for body surface potential mapping [14] we chose it as an operative base from which to work believing that a reasonable approximation of equivalent dipole moment and locus can be obtained by Gabor Nelson summation over a surface of 140 elements.

When the known electrical source was very simple (i e. a single dipole) its locus and moment were easily and accurately estimated both by the summation method and by the lead vector search procedure.

The relative computation times for a single instantaneous dipole were 15 seconds by summation (of 140 electrode values) and 180 to 200 seconds by lead vector search whether 7 or 28 electrode values were used With voltages of more complex origin (double dipole or live data) the computation times remained roughly the same However departure of the results of lead vector search from Gabor Nelson estimates increased with an increase in noise level a decrease in electrode number or an increase in complexity of the electrical source

It is interesting that the great difficulty came in the assay of the locus of the equivalent dipole but not in the assay of moment This would suggest that various corrected clinical vectorcardiographic sys-

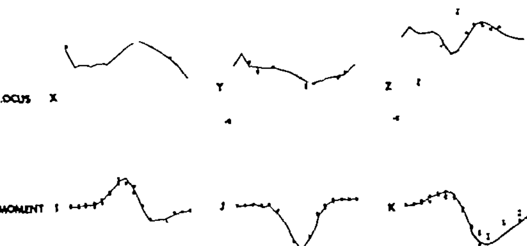


Fig 3 Results of estimates ith 7 20, and 28 electrodes by representing locus nd moment in term of scala lead components.

Table I Est mate of relative size of error vectors

	Integration (Gabor Nelson)		*Lead-vector search (Helm-Chen)*					
			28 sites		*20 sites*		*7 sites*	
	Locus	*Moment*	*Locus*	*Moment*	*Locus*	*Moment*	*Locus*	*Moment*
Single dipole (L) 1-8	0 032	0 010	0 028	0 003	0 069	0 022	0 076	0 003
+ 1 % noise	0 032	0 010	0 044	0 006	0 071	0 010	0 040	0 009
+ 5 noise	0 044	0 014	0 185	0 048	0 326	0 112	0 301	0 065
Double d pole (L + R) 2-7			0 201	0 062	0 392	0 229	0 615	0 180
+ 1% noise			0 205	0 059	0 398	0 230	0 613	0 176
+ 5% noise			0 231	0 061	0 402	0 235	0 608	0 184
Distributed generator ("live data) 1 90 msec			0 658	0 398	0 598	0 352	1 217	0 337

tems should be able to display equivalent moment rather well despite l m ted num bers of electrodes and superimposed noise from adverse recording conditions. It would also suggest that searching for the locus which produces the least error m reproducing surface voltages by lead vector equations may run into serious trouble under certain circumstances. In our data this occurred when the original electrical source did not reside in a single point and therefore a single set of lead vectors was not appropriate A possible consequence of a distributed source with many lead vectors from many sites operative during voltage generation would be that the error by which the later search was guided was lumpily distributed in the volume of search, thus leading to faulty answers.

These theoretical considerations are worthy of study but practical biological application is confronted by conflicting choices (1) Rapid machine computation of equiv

Table IA Recalculation of estimate of error by lead vector search (with new equations of Helm and Chou)

	28 sites		*20 sites*		*7 sites*	
	Locus	*Moment*	*Locus*	*Moment*	*Locus*	*Moment*
Single dipole (L) 1-8	0 000	0 000	0 000	0 000	0 003	0 000
+ 1% noise	0 010	0 006	0 017	0 006	0 035	0 010
+ 5% noise	0 061	0 022	0 114	0 024	0 183	0 055
Double dipole (L + R) 2 7	0 143	0 040	0 308	0 149	0 507	0 088
+ 1% noise	0 201	0 030	0 307	0 149	0 507	0 108
+ 5% noise	0 195	0 079	0 310	0 147	0 542	0 124
Distributed generator ("live" data) 1 90 msec	0 544	0 214	0 651	0 325	0 914	0 330

*When all 140 electrodes were utilized the error estimates for locus and moment fell to 0.405 and 0.108 respectively

alent dipole moment and locus by summation is feasible if a large number of simultaneous voltages are recorded this makes recording on a clinical scale cumbersome and limited (2) Rapid recording with a limited number of electrodes is clinically feasible and analog (VCG) approximation of moment is rather good however digital approximation of locus and moment by lead vector search is slow and the locus values appear not satisfactorily reliable from these data The slower computation time with lead vector search is exaggerated in this study because the lead vectors at each test site had to be computed instead of called from storage as Helm and Chou[11] recommended If these were readily available computation would certainly be more rapid * It seems probable that a reasonable clinical approximation of the moving dipole may be evolved from these beginnings by a compromise between the slow recording fast-computing summation approach and the fast recording slow-computing lead vector search The fact that rather good approximations of moment are already available instantaneously in the form of vectorcardiograms may provide the constraint needed to work out such a compromise

*A word of caution is appropriate here Search within a cubic volume (10 cm. on each edge) with test sites 1 mm. apart would require storage of 1 million coefficients per surface electrode or an absolute minimum of 4 million values. An alternative is obviously desirable.

Summary

Two methods of recovering the equivalent dipole of variable locus and moment from voltages of 140 or fewer surface recording sites have been examined (1) summation of all available elements (Gabor and Nelson[9]) and (2) lead vector search (Helm and Chou[11]) Summation requires many recording sites but is rapidly done on a digital computer whereas lead vector search requires fewer recording sites but involves much longer computing times.

Recovery of a single noise-free factitial input dipole by summating over 140 points was good as to locus and moment. Recovery by lead vector search was also good whether 7 or 28 electrodes were employed

Increasing error of estimation—especially of locus—was noted however with the lead vector search with (1) increasing the noise level (2) diminishing the number of electrode sites (from 28 to 20 to 7) and (3) increasing the complexity of the generator (from single dipole input to double dipole input to live data)

Clinical application awaits improved methodology—perhaps by compromise between slow recording fast-computing summation and fast recording slow-computing lead vector search

Addendum

Since completion of this manuscript Dr Robert A. Helm called to our attention the

modification of the original equations of Helm and Chou. The new equations were reported at the Vectorcardiographic Symposium in New York, May 17, 1970 (Helm, R. A., and Chou, T. C.: The use of a variably located dipole as an equivalent generator, presented at the XI International Symposium on Vectorcardiography, sponsored by the Long Island Jewish Medical Center, New Hyde Park, N. Y., May 15 to 17, 1970. In press.) They correspond to the original equations except that multiplication of each element by the electrode voltage or its square permits "weighting" of the total effect in favor of leads with large voltages. Therefore, they theoretically should produce a more realistic reflection of the net effect of a distributed source. Calculations are also simpler and quicker.

We have recalculated the results shown in Table I and have noted dramatic reduction in the estimation of error for the single factitial dipole and considerable improvement also for the dipole pair. However, although significant improvement for the distributed generator also occurred, it was not as great. Thus, the new findings strengthen interest in this approach but indicate the need for further sophistication for handling of "live" data.

The assistance of Mr. Carey Miller and Mr. Tom Hitt in the preparation of data and in computer programming is gratefully acknowledged. Mrs. Pat Orander assisted in recording the live data and in the preparation of the illustrations.

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Appendix

The search procedure assumes an initial locus of the equivalent dipole. The dipolar moment at that locus which gives the least deviation from known surface voltages is computed from simultaneous equations (Equations 11 to 13 of Helm and Chou[1]). These result from dividing the basic Burger lead vector equations for each surface voltage (including error elements in each equation) by the surface voltage, then squaring and summating. The partial derivative of the sum of the error (squares of the quotients) divided by the voltage is taken with respect to each coordinate of moment. In matrix form these equations condense (when the sum of the squares of error voltage are set to zero) to the form

$$\overset{(3 \times 1)}{D} = \overset{(3 \times 3)}{C}\overset{(3 \times 1)}{M}$$

where vector D is composed of the sums of the quotients of lead vector coordinates divided by lead voltages, matrix C is the

autocorrelation matrix of such quotients and M represents the desired coordinates of moment An estimate of relative error (i e sum of squares of the quotients of error voltage) is obtained from Equation 7 of Helm and Chou[11] (This is in effect the number of electrodes minus twice the dot product of D and M plus the sum of the products resulting from multiplying each element of C by the corresponding element of an autocorrelation matrix of M)

Then errors from trials resulting from moving the locus 1 unit in each direction (± X Y or Z) are compared If improvement occurs the better locus is chosen if not the size of the unit of search is reduced and a finer-grained search is made within the immediate locality

Teaching selective attention to the cardiac cycle The Cardio-gater

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Donald J. Campbell, B.S.E.E.
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In learning cardiac auscultation the most difficult skill to acquire is *selective attention* to the separate audible components of the cardiac cycle. *Selective attention* is essential to correct diagnosis when the auscultatory problem is complex, that is, when several sounds and murmurs occur in rapid sequence.

The skilled clinician is trained to "block out" deliberately all but a portion of the cardiac cycle and to concentrate his attention on that portion. He times the first heart sound with the carotid pulse or the apical impulse and selectively and sequentially listens to the first half of systole, the second half of systole, and then first, middle, and final thirds of diastole.

We have designed and tested an instrument called the Cardio-gater which allows the instructor or student to visually "gate in" or "gate out" any selected portion of the cardiac cycle. The student's attention is directed to those sounds and murmurs occurring in that portion of the cardiac cycle because the remainder of the cycle is silent. The selected sounds can be returned to context by adding the remainder of the cardiac cycle.

The purpose of this report is to relate our experience with the Cardio-gater as a useful audiovisual aid in the teaching of heart sounds and murmurs.

Methods

The term *gate* is used to describe an electronic circuit which can selectively pass or stop a signal. An electronic gate is analogous to a soundproof door interposed between a listener and a speaker. When the door is open sound passes to the listener, but when the door is closed no sound is transmitted. Unlike the door, the electronic gate is opened or closed instantaneously and can pass or stop sounds with a duration of less than 0.01 second. Distracting sounds would be created if the door of our analogy squeaks or closes with a thud. Electronic gating circuits may similarly introduce adventitial clicks or thumps. This difficult engineering problem was solved by the use of a field effect transistor in the gate circuit. The operation of this transistor has been carefully controlled so that it opens and closes the gate at just the right speed. If the gate were to open too rapidly, a thump would be produced; if too slowly, the initial sound transmitted would be muffled.

Circuitry and operation. A block diagram

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Fig. 1 Block diagram of the essential electronic features of the Cardio-gater

Fig. 2 The operational features of the Cardio-gater: (A) Heart rate meter (B) triggering level control (C) triggering slope switch (D) *Start* and (E) *Stop* time dials which set the time intervals from the trigger point to the start and stop of the gate, (F) switch which sets the polarity of the gate, (G) fader control, (H) low tick, and (I) high tick dials which set the time interval between the trigger point and an audible tick of low or high pitch.

of the essential electronic features of the Cardio-gater is shown in Fig 1 The operational features are shown in Fig. 2. A *heart rate meter* (*A*) is calibrated for both heart rate and R R interval. The meter is useful in determining when the triggering controls have been adjusted properly The *triggering controls* *B* and *C*, must be set appropriately for each patient's QRS complex. Ordinarily the triggering level (*B*) is set higher than the peaks of the P T and Q waves. Either the positive or negative slope of the R wave may be used for triggering (*C*) The *time dials* marked *Start* (*D*) and *Stop* (*E*) set the time interval from the trigger point to the start and stop of the gate. The *Start* dial may be set for any interval less than the R R interval as recorded on the meter The time interval from the trigger point to a gated sound can be read directly on the dial in milliseconds. A switch (*F*) sets the polarity of the gate A positive gate passes heart sounds only during the gated period whereas a negative gate passes sounds only during the ungated period. Since it is not possible to set the stop dial very close to the end of the R R interval the negative gate may be used for presystolic audible events.

Another use of the negative gate is to eliminate or attenuate a particular sound. The control marked *Normal-Gated* is the *fader control* (*G*) In the *Normal* position the output and input signals are identical and no gating is effected even though the device is triggering. In the *Gated* position the output is a gated version of the input. This control makes it possible to take a portion of the auscultation which has been isolated and gradually bring it back into the context of the entire auscultation Another use of the fader control is to provide a weak background of nongated heart sounds in conjunction with heart sounds emphasized by gating so that the listener perceives the position of the gated sounds in the cardiac cycle. The time dials labeled *Low tick* (*H*) and *High tick* (*I*) set the time interval between the trigger point and the audible tick of low or high pitch These dials are independent of the start and stop dials. A tick can be set to occur at anytime in the cardiac cycle and is independent of the gating operation. The switches in the row marked *Z* turn on the *intensity display* for the gated portion of the cardiac cycle or the ticks.

Visual displays The teaching impact of the Cardio-gater is heightened by the use of visual displays simultaneously with the aural presentation The visual displays use intensity modulation of a modified Hewlett Packard multitrace oscilloscope (Model 769 A) to show which portion of the phonocardiogram is being gated in or out. The following visual displays were available (1) electrocardiogram, (2) the ungated phonocardiogram, (3) the gated portion brighter than the ungated portion (4) the gated portion alone (5) the gated portion indicated by an adjacent bar or bracket, and (6) a movable vertical line to serve as a visual pointer All visual displays are triggered so that auditory events always appear at about the same location on the oscilloscopic monitor (Figs. 3 to 7) The tick can be inserted anywhere in the cardiac cycle to act as an aural pointer In the visual display the tick appears as a vertical line

Specifications The time interval between the trigger point and the onset of the gate is continuously variable between 10 and 1,500 msec. The heart rate meter is calibrated in beats per minute (40 to 120) and R R interval *in milliseconds* (*500 to* 1,500 msec.) The electrocardiogram (ECG) triggering range is ± 2 volts (high range) or ± 0.8 volts (low range) ECG triggering input impedance is 70 kilo-ohms (kohm.) Phonocardiographic voltage gain is 2 phonocardiographic input impedance is 30 kohm phonocardiographic output is 3.8 volts R.M.S into a 400 ohm load and will drive at least 40 stethophones total harmonic distortion is 1.2 per cent. Tick frequencies are 600 and 320 Hz. Trigger output is a -15 volt pulse followed in 1.8 msec. by a $+8$ volt pulse.

Patient material. The Cardio-gater has been used in the teaching of medical students, house staff members, and graduate physicians. Heart sounds and murmurs may be obtained directly from patients or from prerecorded tapes. Auscultation is with stethophones. All recordings were made

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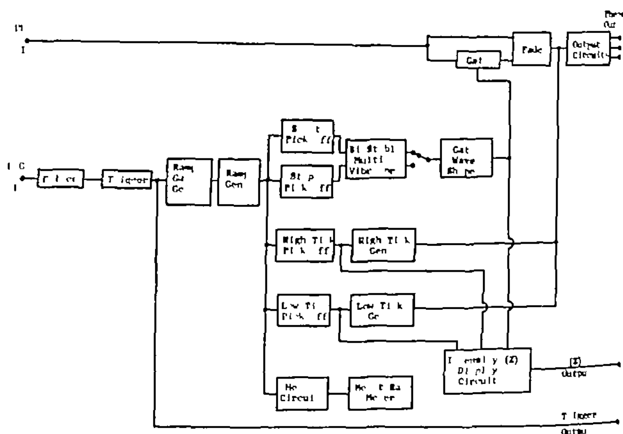


Fig *1* Block diagram of the essential electronic features of the Cardio-gater

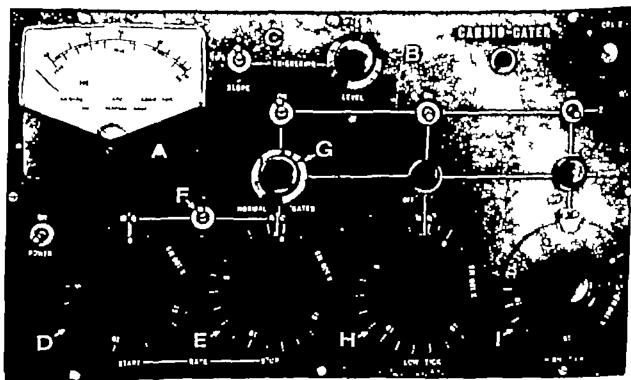


Fig *2* The operational features of the Cardio-gater: (*A*) Heart rate meter (*B*) triggering level control (*C*) triggering slope switch (*D*) *Start* and (*E*) *Stop* time dials which set the time interval from the trigger point to the *start* and stop of the gate (*F*) switch which sets the polarity of the gate, (*G*) fader control (*H*) low tick, and (*I*) high tick dials which set the time interval between the trigger point and an audible tick of low or high pitch.

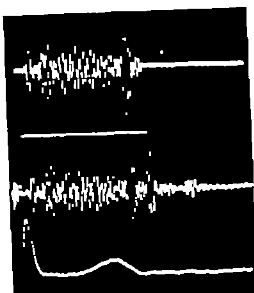


Fig. 5 Recording made at left midsternal edge. Pulmonic closure has been gated out (second trace from top) and the pansystolic murmur of mitral insufficiency ending with aortic closure was heard (top trace).

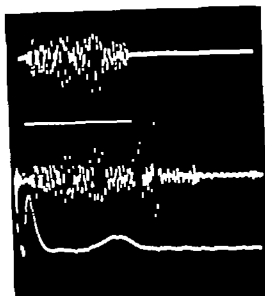


Fig. 6 Recording made at left midsternal edge. Aortic closure has been gated out (second trace from top) leaving only the pansystolic murmur (top trace)

since the patient was 16 years old At age 23 she was successfully treated for bacterial endocarditis. On that admission a very loud apical systolic murmur was heard The murmur was transmitted to the top of the head the lumbar spine and less loudly to the base of the heart. A left ventriculogram showed high-grade mitral insufficiency Left ventricular end-diastolic pressure was 24 mm. Hg A regurgitant wave of 59 mm Hg was recorded in the left atrium. Pulmonary artery pressure was 35/16 with a mean pressure of 22 mm. Hg The clinical diagnosis was ruptured chordae tendineae superimposed on rheumatic mitral valve disease.

The Cardio-gater was used in this case to unravel a difficult auscultation for the student. In all illustrations (Figs. 3 to 7) the gated phonocardiogram is on top the interval of the gate below it, the ungated phonocardiogram below that, and the triggered ECG is the bottom trace

The first recording was made at the cardiac apex (Fig 3) Following the murmur there was a silent interval followed by a loud sound. Note that the loud sound was a third sound gallop (S_3) which occurred after the T wave of the ECG Since aortic valve closure at the apex was obscured by

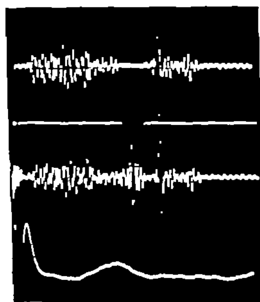
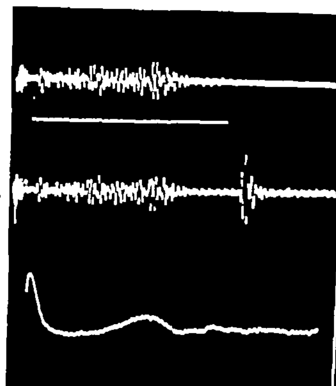


Fig. 7 Recording made at the left midsternal edge. The ease of gating an individual sound is demonstrated. Aortic closure has been selectively gated out (top two traces).

the pansystolic murmur the auscultation simulated an ejection systolic murmur followed by a loud aortic closure sound. The Cardio-gater was used to clarify this auscultatory illusion.

Fig 3



Fig

Fig 3 This recording was made at the cardiac apex in a patient with ruptured chordae tendineae (see text for details) The gated phonocardiogram is on top, the interval of the gate below it the ungated phonocardiogram below that, and the triggered ECG is the bottom trace Following the murmur there was a silent interval followed by a loud sound (third trace from the top) The loud sound was a third sound gallop (S_3) which occurred after the T wave of the ECG Since aortic valve closure was obscured by the pansystolic murmur the auscultation simulated an ejection systolic murmur followed by a loud aortic closure sound. The Cardio-gater was used to clarify this auscultatory illusion. The loud S gallop was gated out (second trace from the top) and the murmur was more typically pansystolic (top trace)

Fig 4 The recording was made at the left midsternal edge Three distinct sounds could be heard following the murmur aortic closure pulmonic closure, and a third sound gallop which was less loud in this location (third trace from top) The S_3 gallop was selectively gated out (second trace from top) and wide constant splitting of the second heart sound could be appreciated (top trace)

with the patient in the supine position during normal continuous respiration Heart sounds were recorded with the use of a Hewlett Packard/Sanborn* contact microphone (Model 350 1700-C10) and a Hewlett Packard heart sound preamplifier (Model 350-1700 B) An ECG was simultaneously recorded with a Hewlett Packard high gain preamplifier (Model 350-2700 C) Heart sounds and the ECG were recorded on a dual channel Crown† magnetic tape recorder (Model SX 700) The ECG was recorded on an AM tape channel converted to FM with the use of an A. R Vetter‡ FM recording adaptor (Model 2) Frequency response of the FM conversion was 0 to 1 000 c.p s.

*Sanborn Division of Hewlett Packard Corp., Waltham, Mass.
†Crown International, Inc Elkhart, Ind.
‡A. R. Vetter Co., Rebersburg, Penn.

Results

The Cardio-gater has been used in the teaching of medical students house staff members, and graduate physicians during the past three years. The technique lends itself to either individual self teaching or large classroom instruction The instrument has proved particularly useful in the following situations (1) recognition and interpretation of a soft sound that is masked by a louder sound or murmur (2) differentiation of a pansystolic murmur from a long ejection systolic murmur and (3) demonstration to the student of the value and technique of selective attention to the cardiac cycle

The value of the Cardio-gater in teaching selective attention to the cardiac cycle is demonstrated in a 25 year-old patient (Figs. 3 to 7) A soft apical pansystolic murmur was known to have b

gater allows the instructor or student to visually "gate in" or "gate out" any selected portion of the cardiac cycle. Attention is directed to those sounds and murmurs occurring in the selected portion of the cardiac cycle because the remainder of the cycle is silent. The selected sounds can be returned to context by adding the remainder of the cardiac cycle. Design considerations permit noiseless operation of the gating circuit. The teaching value of the device is increased by the use of several visual displays simultaneously with the aural presentation. The technique lends itself to either individual self teaching or classroom instruction. The instrument has proved particularly useful in the recognition and interpretation of a soft sound that is masked by a louder sound or murmur and in the characterization of systolic murmurs.

REFERENCE

1 Levine, S. A., and Harvey, W. P.: Clinical auscultation of the heart, Philadelphia, 1949, W. B. Saunders Company, p. 5

In Fig. 3 the loud S_3 gallop was gated out and the murmur was more typically pansystolic. If the gate were only partially opened at the time of the S_3 gallop its intensity could be effectively decreased. (This demonstrates the ability of the device to reduce the intensity of a single sound.)

The recording site was then moved to the left midsternal edge. Three distinct sounds could be heard following the murmur: aortic closure, pulmonic closure, and a third sound gallop which was less loud in this location (Fig. 4). The S_3 gallop was selectively gated out and wide constant splitting of the second heart sound could be appreciated (Fig. 4). Pulmonic closure was then gated out and the pansystolic murmur of mitral insufficiency ending with aortic closure was heard (Fig. 5). Aortic closure was gated out leaving only the pansystolic murmur (Fig. 6).

The ease of gating an individual sound is demonstrated in Fig. 7. Aortic closure sound has been selectively gated out.

Discussion

The Cardio-gater has been used for three years at the University of Cincinnati College of Medicine in teaching auscultation to students, house staff members, and graduate physicians. The technique has been subjectively evaluated by staff cardiologists. They have thought that student performance in cardiac examination has been improved. The students have accepted the technique with some enthusiasm. Electronic gating of heart sounds has been utilized in both individual self-teaching and large classroom instruction, with the use of both patients and prerecorded tapes. Recent experience with programmed self-teaching tapes with gated heart sounds has been very encouraging. Selected sounds have been returned to context by adding the remainder of the auscultation.

Experience with the Cardio-gater has defined situations in which gating is particularly useful. We have found it useful in the recognition of a relatively soft sound that is masked by a louder sound or murmur which closely follows or precedes it. Antegrade and retrograde masking of heart sounds are well recognized clinical difficulties. Examples include a fourth sound gallop masked by a loud first heart sound (S_1), splitting of S_1 obscured by a loud mitral closure sound, mitral or aortic closure sounds masked by a loud pansystolic murmur, and masking of a split S_2 by either a loud aortic or pulmonic closure sound.

The Cardio-gater has proved useful in differentiation of a pansystolic murmur from a long ejection murmur. Selective attention to the end of systole and early diastole helps to clarify two not infrequent auscultatory illusions. A long systolic ejection murmur of aortic closure sound (A_2) must be differentiated from the pansystolic murmur of mitral insufficiency. A loud pansystolic murmur which masks a normal A_2 and is followed by an audible S_3 must be differentiated from a long systolic ejection murmur followed by A_2.

The Cardio-gater has also proved useful in defining a mid or late systolic click followed by a later systolic murmur. The student often confuses the click with A_2, the late systolic murmur with an early diastolic murmur, and A_2 with an S_3 gallop.

Certain difficulties arise in demonstrating late diastolic events when atrial fibrillation and variation in R-R interval are present. It is difficult to set the boundaries of the gate under these circumstances. If a QRS complex occurs early, e.g., after the gate opens, but before the gate was set to close, the gate will fail to close and all of the auscultation occurring in the next cardiac cycle will be transmitted. This problem can be obviated by the use of a negative gate which is set to be open during all of the cardiac cycle preceding a presystolic murmur. No sound is passed while the negative gate is open. Since the next QRS complex occurs after the gate was set to close, all of the presystolic murmur (and only that interval) will be heard.

The value of electronic gating of heart sounds and murmurs in teaching selective attention to the cardiac cycle must await more extensive trial and objective evaluation of student performance in this important clinical skill.

Summary

An electronic gating device, the Cardio-gater, has been used to teach selective attention to the cardiac cycle. The Cardio-

gater allows the instructor or student to visually gate in or gate out any selected portion of the cardiac cycle. Attention is directed to those sounds and murmurs occurring in the selected portion of the cardiac cycle because the remainder of the cycle is silent. The selected sounds can be returned to context by adding the remainder of the cardiac cycle. Design considerations permit noiseless operation of the gating circuit. The teaching value of the device is increased by the use of several visual displays simultaneously with the aural presentation. The technique lends itself to either individual self-teaching or classroom instruction. The instrument has proved particularly useful in the recognition and interpretation of a soft sound that is masked by a louder sound or murmur and in the characterization of systolic murmurs.

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Summary

An electronic gating device, the Cardio-gater, has been used to teach selective attention to the cardiac cycle. The Cardio-

and arterioles along the segment of limb introduced into the plethysmographic container. Tracings obtained from an entire limb for these reasons, will tend to be distorted. Therefore the use of a smaller limb segment as the finger will provide better demarcations of the curve because it offers a shorter distance for pulse waves to travel within the plethysmographic container.

This technique does not however exclude other factors such as elasticity of the arterial walls inertial forces, viscosity of the blood and so forth which progressively alter the shape of the central pulse wave to a greater degree in the periphery of the vascular tree.

For these reasons, despite the use of a small limb segment to obtain the pulse curve the technique of measurement (to be described) differs from that used to measure systolic intervals in the carotid pulse tracing.

Instruments

An Elema Schönander crystal transducer (Model EMT 510 C) was used to obtain the plethysmograms. The time constant of the instrument varies with the sensitivity setting (2 seconds at the lowest and 4 seconds at the highest sensitivity). The finger cup which is air filled has a capacity of 18 ml the chamber 0 75 ml and the connecting tube, 3 3 ml making a total volume of 22 ml when the finger is not in the cup. Calibration may be obtained by means of a calibration button which introduces into the system a defined volume of air (0 1 ml).

A Sanborn crystal transducer was used to record the simultaneous carotid pulsations. All transducers were fed into an 8 channel Sanborn photographic polygraph (Model 568-100 A).

Subjects

The study was done on a group of 10 healthy male volunteers, aged 24 to 32 years.

Methods

At least 10 consecutive beats were recorded during relaxed expiratory apnea with the subject in a recumbent position.

Digital plethysmograms were obtained from the second or third finger of the left hand with simultaneous recording of Lead II of the electrocardiogram a phonocardiogram (at the third left intercostal space with nominal filter at 50 Hz) and the right carotid pulse.

Comparative readings of carotid and plethysmographic ejection times were made by three mutually blinded observers in the following manner. After successively numbering 10 beats in each strip the first two observers were assigned either the odd-numbered or the even-numbered beats the third observer read the odd numbered beats in half of the patients and the even numbered beats in the remaining half.

The observers located the points of beginning of the upstroke and incisura (dicrotic notch) on both the carotid and plethysmographic tracings in their assigned beats as follows. On the carotid curve the LVET was measured from the initial change of speed of displacement (where the upstroke changes from thick to thin) to the nadir of the incisura.[6,7]

The beginning of the upstroke and incisura of the plethysmographic tracing were determined by extrapolation of the rapid ascent of the curve for the former and extrapolation of the most rapid descent prior to the dicrotic notch for the latter. This was found empirically to give the best landmarks of measurement (Fig 1 A).

"Blinding" of the observers was achieved by doing the actual measurements of the intervals in a second step once all the points were placed in the assigned beats for each subject.

The pulse transmission time was measured from the aortic component of the second heart sound (initiation of its first high-frequency deflection) to a point in the plethysmographic tracing, which is called d considered analogous to the carotid incisura, due to the proximity to the dicrotic notch of the volume curve (Fig 1 B). The velocity of the pulse wave was calculated by dividing the distance travelled (measured from the sternal notch to the fingertips) by the mean pulse transmission time of each subject (determined from the plethysmographic tracing).

Measurement of the left ventricular ejection time by digital plethysmography

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*David H. Spodick M.D.****
Boston Mass.

The volume changes of the extremities due to variations of flow and pressure within the vessels have been extensively studied for almost a century and multiple publications appear in the medical literature assessing the value of the plethysmograph as a diagnostic tool for peripheral vascular diseases.[1-4] Most of the studies were related to the amplitude and shape of the plethysmographic pulse wave and its velocity of transmission.

This paper will describe a technique for measuring the left ventricular ejection time from the digital plethysmogram attempting by means of a peripheral phenomenon to evaluate an aspect of cardiac function which is conventionally measured from a central pulse curve.

The importance of the left ventricular ejection time (LVET) derived from non-invasive techniques as a parameter of ventricular performance has been clearly demonstrated.[5-11] The usefulness of this parameter and the inherent difficulties of obtaining it in patients with marked respiratory distress tracheostomy or extreme obesity forced us to look for an alternate way of accurately obtaining the ejection period when a good carotid pulse phonocardiogram and/or apexcardiogram are not available. In the present study we regarded the carotid-derived ejection period as the standard of comparison as established in a previous publication.[8]

The systolic pulsations of the peripheral arteries and arterioles produce volume changes of the extremities which can be easily recorded at almost all levels of the vascular tree with any of the types of plethysmograph available.[9-11]

The time of transmission of the pulse wave increases with the length of the limb over which the pulse is reflected.[2] This is manifested by the delay in the onset (and hence subsequent points) of the more distally recorded pulse wave as compared to a simultaneously obtained proximal tracing.

When a plethysmogram is recorded in a particular limb the volume changes indicated would theoretically reflect the resultant of the volume curves of all the arteries

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Table I Numerical results

Subject	Tracings	Observer 1: ½ selected beats 1	3	5	7	9	x̄	Observer 2: 2	4	6	8	10	x̄	Observer 3: 1	3	5	7	9	x̄
1	C*	280	290	290	290	290	288	290	290	280	290	280	286	290	280	280	290	290	286
	P*	280	300	305	290	310	297	300	290	280	290	270	286	290	270	260	280	290	278
														2	4	6	8	10	x̄
2	C	310	320	310	300	320	312	315	320	320	300	325	316	310	320	310	300	320	312
	P	310	325	310	310	310	313	310	315	320	300	320	313	300	305	310	295	310	304
														1	3	5	7	9	x̄
3	C	280	290	270	280	280	280	280	280	280	280	280	280	280	280	280	280	280	280
	P	295	290	285	290	290	290	270	285	285	300	280	284	295	295	280	280	280	286
														2	4	6	8	10	x̄
4	C	290	300	290	290	290	292	290	285	280	295	285	287	290	290	290	290	290	290
	P	295	295	300	300	300	298	295	285	290	290	290	290	285	290	290	295	300	292
														1	3	5	7	9	x̄
5	C	310	310	300	300	295	303	305	300	300	300	295	300	320	310	305	295	295	305
	P	305	305	300	295	295	300	300	290	290	280	290	290	310	290	285	295	300	296
														2	4	6	8	10	x̄
6	C	300	290	300	300	285	295	290	305	280	295	290	292	280	300	300	290	280	290
	P	290	290	300	305	270	291	280	300	280	300	300	292	300	310	310	280	270	291
														1	3	5	7	9	x̄
7	C	270	270	275	270	265	270	285	270	280	275	280	278	285	270	275	280	260	274
	P	270	260	280	275	260	269	280	270	270	265	270	271	270	260	260	260	250	60
														2	4	6	8	10	x̄
8	C	280	270	280	280	280	278	280	285	285	275	270	279	280	280	280	270	270	276
	P	290	270	270	285	280	279	290	285	280	280	270	281	280	270	2 0	270	270	72
														1	3	5	7	9	x̄
9	C	265	270	65	260	260	264	275	280	260	255	270	268	270	270	260	260	260	264
	P	265	285	270	280	270	274	270	280	265	250	265	266	260	270	260	270	260	264
														2	4	6	8	10	x̄
10	C	290	280	270	270	285	279	280	280	265	280	285	278	280	290	270	290	280	282
	P	290	275	275	280	283	281	270	275	260	283	280	274	270	280	270	290	280	2 8

*C = Carotid-derived LVET. P = plethysmogram-derived LVET

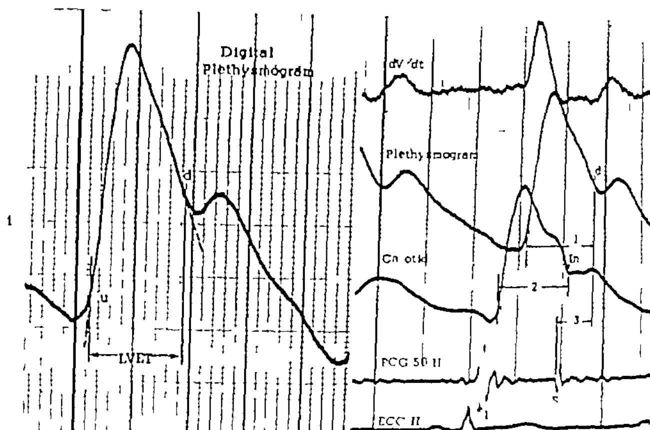


Fig 1 A Digital plethysmographic tracing showing the technique of extrapolation to obtain the *u* (upstroke) and *d* points. These landmarks are located at the points where the extrapolated (dotted) lines separate from the curve B Typical polygraphic tracing showing from top to bottom *dV/dt*, first derivative of the digital plethysmogram digital plethysmogram carotid pulse tracing phonocardiogram and Lead II of the ECG *1* = Plethysmogram-derived left ventricular ejection time *2* = carotid-derived left ventricular ejection time and *3* = peripheral pulse transmission time

Results

Three hundred measurements of ejection periods were made from both the carotid and plethysmographic tracings (Table I)

Table II shows the analysis of variance. It indicates no significant difference between the values of ejection time obtained from the carotid pulse and from the plethysmogram It also shows a highly significant difference between patients which is expected due to the different values of LVET and different heart rates. There is a barely statistically significant difference (P~0 05) between observers for all the measurements, which is of no practical importance due to its small value and is confounded with beat to beat differences if any

The mean carotid-derived LVET (286 ± 16 1 S D *) was very close to the mean plethysmogram-derived LVET (285 ± 15 6 S D) the residual S D of a single measurement is 8 1 msec and the S E.* of prediction 3 8 msec

Fig 2 shows the correlation of values (r = 0 88) the 45 degree solid line represents an ideal correlation (r = 1) and the two dotted lines the limits of 1 residual S D of a single measurement (8 1 msec.)

In this group of young and healthy individuals the mean pulse transmission time to the finger was 149 ± 17 msec and the mean velocity 6 24 ± 1 49 M per second

*S.D Standard deviation; S.E., standard error

Discussion

The r value of 0 88 for the measurements of ejection periods indicates a high degree of correlation between the carotid and plethysmographic tracing (Fig 2) This however would have been even better if the influence of the natural scatter of ejection periods for different heart rates, individuals and observers was smaller

*S.D Standard deviation; S.D., standard error

2 The mean pulse wave velocity calculated from the peripheral pulse transmission time (measured from the aortic component of the second heart sound to the *d* point of the plethysmogram) is comparable to the pulse wave velocity determined by other methods.

Summary

A blinded multiple-observer comparison of ejection periods obtained from simultaneous carotid pulse tracings and digital plethysmograms was made in 10 healthy volunteers.

The technique for measuring the left ventricular ejection time from the plethysmographic curve consists of the extrapolation of the rapid ascent toward the base line to obtain the upstroke point (*u*) and extrapolation of the rapid descent, preceding the dicrotic notch to obtain the *d* point, analogous to the carotid incisura.

A high degree of correlation with a high reciprocal predictability was found for both methods of obtaining the ejection time

The mean value of peripheral pulse transmission velocity was found to be in close agreement with those obtained by other investigators

We express our gratitude to Hugo Muench, M.D., D.Sc., of the Department of Biostatistics, for his invaluable assistance in the statistical analyses.

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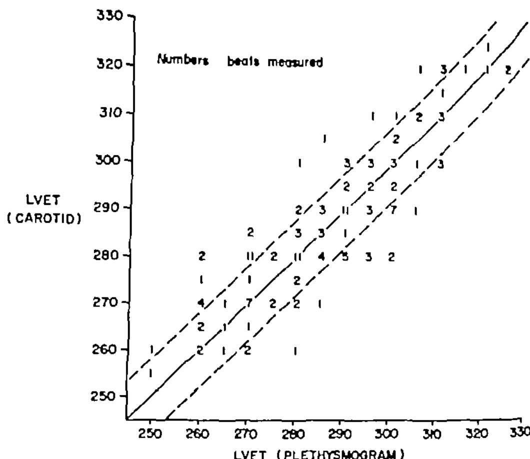


Fig. 2 Correlation of values LVET Left ventricular ejection time expressed in milliseconds. The solid line is an ideal correlation with an r value of 1 The two dashed lines represent the limits of 1 residual S.D (± 8.1 msec.) of an individual measurement

Table II *Analysis of variance**

Source of variance	*Sum of squares*	*Degrees of freedom*	*Mean square*	*F ratio*	*P value*
Total	69 325	299			
Patients	49 934	9	5 548	84 8	0 001
Examiners	589	2	294	4 5	0 05
Interaction (carotid plethysmogram)	44	1	44	0 67	
Remainder	18 758	287	65 4		

Residual S.D of single measurement $\sqrt{65.4} = 8.1$ msec S.E. of prediction $\sqrt{S.D\ (1-r^2)}$ 3.8 msec.

(giving consequently smaller standard deviations)

Considering that the residual standard error of the measurements was 3 8 msec. if we obtain the ejection periods in a given number of patients by means of the digital plethysmogram 95 per cent of the measurements will be within ±7 6 msec. (2 S E) of the values obtained through a simultaneous carotid pulse tracing

The pulse transmission velocity obtained by this method (6 74 ± 1 49 M per second) is in close agreement with values obtained by other authors in similar groups of subjects with the use of different techniques. The mean values in those studies were 6 95 M per second (±0 79 S D)[3] and 6 48 M per second [14]

Conclusions

1 Digital plethysmography provides a reliable way to measure the e od

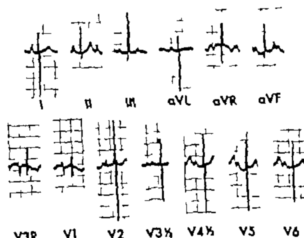


Fig. 1 Standard electrocardiogram of Patient N. N. (No. 7550') taken on Oct. 14 1969. Usual sensitivity of 1 mv = 10 mm. is used except in V and V where one half the standardization is used. There is sinus tachycardia with rate of 140 per minute. The frontal plane axis is about +120 degrees. Peaked P waves are seen in the limb leads and sharply biphasic P waves in the right precordi l leads suggesting bi- trial enlargement.

tion. There was systemic pressure in the right ventricle both in the body and in the outflow tract. A pressure pullback from the pulmonary artery localized severe stenosis t pulmonary valve level. A atrial septal defect was crossed and an oxygen series suggested significa t right-to-left shunting proba bly t both atrial nd ventricular levels with left atrial saturation of 75 per cent nd an ascending aorta saturation of 61 per cent. Right ventricular biplane cineangiography demonstrated double-outlet right ventricle with valvular pulmonary stenosis and infundibular hypertrophy. A main pulmonary artery cineangiogram demonstrated no filling of the right pulmonary artery (Fig. 3). Aortic root biplane cineangiography demonstrated right aortic arch with filling of the right pulmonary artery from right persistent ductus arteriosus (Fig. 4). It was decided that the patient poor clinical condition was predominantly the result of extremely inadequate pulmonary blood flow and so an emergency shunt procedure to the left pulmonary artery was recommended.

The child underwent successful left Blalock-T ussig shunt procedure. However two days later the child suddenly developed respiratory distress and died.

Autopsy revealed double-outlet right ventricle (Fig. 5). There as secundum type atrial septal defect with diameter of 0.7 cm. The ventricular septal defect was 1 cm. in diameter and located in the membranous septum just below the crista supraventricularis. The pulmonary valve was bicuspid and severely stenotic. Moderate inf ndibular hypertrophy was present. The main pulmonary artery gave rise to left pulmonary artery only. A large persistent ductus arteriosus arose from right-sided aortic arch and continued as the right pulmonary artery. The left subclavian to left pulmonary artery shunt was patent. There was massive aspiration ith hospitalized mucous and



Fig. 2 Supine anteroposterior chest x-ray. There is moderate cardiac enlargement with concave main pulmonary artery segment and a tilting upward of the ventricular apex giving the ppearance of a so-called "boot-shaped" heart. The thymic shadow obscures much of the great vessel silhouette. Overall pulmonary vascularity is moderately and symmetrically decreased.

gastrointestinal products in the trachea with complete obstruction of the left main tem bronchus leading to complete telectasis of the left l ng. This latter finding was the probable cause of death. There was an incidental finding of hypoplastic left kidney nd renal artery.

Discussion

Double-outlet right ventricle has been recognized with increasing frequency in

Case reports

Double-outlet right ventricle with origin of right pulmonary artery from a right-sided ductus arteriosus

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Double-outlet right ventricle is an uncommon type of congenital heart disease in which there is partial transposition of the great vessels and both the ascending aorta and pulmonary artery arise entirely from the outflow tract of the right ventricle In addition to the necessary ventricular septal defect many other associated lesions have been reported[1-4] We wish to report a unique case of double-outlet right ventricle with associated severe valvular pulmonary stenosis right aortic arch infracrista ventricular septal defect secundum atrial septal defect and a right pulmonary artery which arose entirely from a right sided persistent ductus arteriosus.

Case report

N N a 10-month-old Negro female infant, was referred to Mou t S nai Hospital for cardiac evaluation She was the product of a normal pregnancy labor nd delivery with a birth weight of 6 pounds 11 ounces. She was cyanotic at b rth and a cardiac murmur was audible within the first 24 hours. Her cl nical course was marked by early onset of frequent severe cyanotic pells leading to frequent emergency admissions to another hospital. She underwent cardiac catheterization at 3 month of age. Systemic pressure was found i the body of the right ventricle with bidirectional sh nting A atrial septal defect was crossed but the pulmonary artery was not entered. A diagnosis of transposition of the great vessels with pulmonary stenosis was suspected An operation was not advised at this time. The patient had a single sign ficant upper respiratory infection requiring treatment with antibiotics in the recent past. Growth and development were severely retarded. Increasing cyanosis, respiratory difficulty and feeding difficulty led to her evaluation at Mount Sinai Hospital

Physical examination revealed a deeply cyanotic female infant with a weight of 11 pounds (below third percentile) and a height of 26 inches (below third percentile) She could not sit alone. The blood pressure in the arms was 120/70 mm Hg with good femoral pulses. Respirations were 30 per minute and somewhat labored A regular pulse of 160 per minute was palpated There was severe clubbing of the fingers and toes. The lungs were clear to auscultation, and there was no peripheral edema. Cardiac examination revealed a significant left parasternal bulge and heave without a palpable thrill. An LV impulse was not palpable. Auscultation revealed a single first sound of normal intensity a loud single second sound, and a soft third heart sound at the lower left sternal border A Grade 2/6 short ejection systolic murmur was heard localized to the left sternal border The remainder of the physical examination was essentially negative. The electrocardiogram showed sinus tachycardia and possible bi-atrial enlargement (Fig 1) Chest x-ray showed moderate cardiomegaly with a "boot-shaped" heart and modest symmetrically decreased pulmonary vascularity (Fig 2) Fluoroscopy revealed a right sided aortic arch The main pulmonary artery trunk was not well visualized.

Cardiac catheterization was repeated at this

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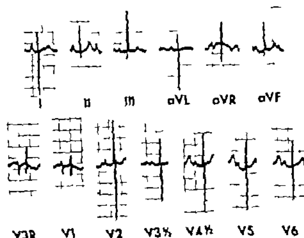


Fig. 1. Standard electrocardiogram of Patient N. N. (No. 75306) taken on Oct. 14, 1969. Usual sensitivity of 1 mv = 10 mm. is used except in V nd V here one half the standardization is used. There is sinus tachycardia with a rate of 140 per minute. The frontal plane axis is abo t +120 degrees. Peaked P waves are seen in the limb leads and sharply biphasic P waves in the right precordial lead suggesting ri trial enlargement.

time. There was systemic pressure in the right ventricle both in the body and in the outflow tract. A pressure pullback from the pulmonary artery localized severe stenosis to pulmonary valve level. An atrial septal defect was crossed and oxygen series suggested significant right-to-left shunting probably at both trial and ventricular levels with left atrial saturation of 75 per cent nd an ascending aorta saturation of 61 per cent. Right ventricular biplane cineangiography demonstr ted double-outlet right ventricle with valvular pulmonary stenosis and infundibular hypertrophy. A main pulmonary artery cineangiogram demonstrated no filling of the right pulmonary artery (Fig. 3). Aortic root biplane cineangiography demonstr ted right aortic arch with filling of the right pulmonary artery from right persistent ductus arteriosus (Fig. 4). It was decided hat the patient poor clinical condition was predominantly the result of extremely inadequate pulmonary blood flow and so an emergency shunt procedure to the left pulmonary artery was recommended.

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Fig. 2. Supine anteroposterior chest x-ray. There is moderate cardiac enlargement with a concave main pulmonary artery segment and a tilting upward of the ventricular apex giving the ppearance of a so-called "boot-shaped" heart. The thymic shadow obscures much of the great vessel silhouette. Over all pulmonary vascularity is moderately and symmetrically decreased.

Discussion

Double-outlet right ventricle has been recognized with increasing frequency in



Fig. 3. Pulmonary cineangiogram. The injection is made into the main pulmonary artery in the anteroposterior position. The left lung vasculature is normal. However, there is a total absence of filling of a right pulmonary artery.



Fig. 4. Aortic root cineangiogram. The lateral projection of an aortic root biplane cineangiogram is illustrated. A large right-sided ductus arteriosus is seen (identified by the arrow) which fills the main right pulmonary artery. The entire right pulmonary bed was seen on subsequent frames.

recent years.[1,7] Most of the patients described have died in infancy or early childhood although survival into the second or third decade has been reported.[6,7] There are several good review articles in the literature.[1-4] This patient belongs in Group 1 A in the classification of Mehrizi.[1]

A large number of associated cardiac and noncardiac lesions have been reported with double-outlet right ventricle. Commonly associated cardiac defects include atrial septal defect, pulmonary stenosis, right aortic arch, patent ductus arteriosus, rudimentary third ventricle, and anomalies of the coronary artery. The pulmonary stenosis is either infundibular, valvular, or both. A bicuspid pulmonary valve is a rather common association.[1] Our patient had both infundibular pulmonary stenosis and severe bicuspid pulmonary valvular stenosis. Right-sided aortic arch, which was present in our case, is also not uncommon with double-outlet right ventricle.[1] Origin of the right pulmonary artery from the aorta is extremely rare. Only a few cases have been reported in the literature.[8,9] To our knowledge, this association has not been described with double-outlet right ventricle.

Embryologically, the right pulmonary artery is formed by the proximal part of the right sixth arch. The distal part of the right sixth arch normally disappears; the corresponding portion of the left sixth arch persists as the ductus arteriosus. When the distal end of the right sixth arch fails to disappear, a right-sided ductus arteriosus results. If i[illegible]



Fig. 5 Postmortem specimen. The right ventricle is displayed in cut section. The aorta is seen to arise entirely from the outflow tract of the right ventricle. The severely stenotic pulmonary valve is also seen. The aortic (*A*) and pulmonary (*PA*) valve leaflets are marked with arrows (→) to illustrate their location at similar levels. The infracrista ventricular septal defect (*VSD*) is also identified by an arrow (→).

tion with the latter the proximal portion of the right sixth arch is interrupted the rare lesion of a right pulmonary artery arising from the aorta as a continuation of the right ductus arteriosus occurs.[8-10] This rare embryologic anomaly has been previously described but not in association with double-outlet right ventricle.[11]

Summary

A patient with double-outlet right ventricle is reported with the heretofore unreported association of a right pulmonary artery arising from a persistent right ductus arteriosus. The patient also had an infracrista ventricular septal defect, a secundum atrial septal defect severe bicuspid valvular pulmonary stenosis, and a right-sided aortic arch

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Obstructed anomalous pulmonary venous return

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Total anomalous pulmonary venous return is an unusual congenital cardiac anomaly of more interest and importance than its incidence might otherwise justify because severe and progressive pulmonary hypertension occurs frequently as a result of obstruction of the anomalous channels. Surgical correction is ordinarily feasible and mandatory if progressive disability and death are to be avoided Unusual variations such as the one described in this report must therefore be recorded to facilitate early recognition and proper management

Two categories of this type of lesion are generally recognized depending upon the termination of the anomalous pulmonary venous channels above or below the diaphragm As a general rule the prognosis is even more grave in the latter instance because of the greater likelihood of severe obstruction The case described herein appears unique displaying characteristics of both supra and infradiaphragmatic varieties The radiographic features are distinctive and may aid in future recognition of similar cases.

Case report

Clinical summary A W a 2 year-old Negro boy was born on June 15 1967 to a 20-year-old primiparous mother after an uneventful pregnancy and delivery He was apparently well until 7 months of age when hospitalized because of bronchopneumonia and heart failure An electrocardiogram revealed right ventricular hypertrophy A diagnosis of total anomalous pulmonary venous drainage with stenosis of the superior vena cava was made at cardiac catheterization. The patient began having syncopal attacks at 14 months of age. He was sent to Charity Hospital of New Orleans at age 22 months for further evaluation.

The child on admission was dyspneic, cyanotic, and edematous. The vital signs were as follows respiratory rate, 45/min. heart rate regular 135/min. and blood pressure, 80/50. There was conspicuous venous distention of the veins of the head neck and upper extremities. Slight clubbing of the fingers and toes was present.

Auscultation revealed a soft systolic murmur at the left sternal border and a soft diastolic murmur at the base. The second sound at the second left i terspace was narrowly spl t and accentuated. The liver was markedly enlarged The electrocardiogram demonstrated right ventricular hypertrophy The chest radiograph showed cardiac enlargement, a prominent superior vena cav and prominent pulmonary vessels. (Fig 1 *A*) The peripheral markings were suggestive of interstitial edema. (Fig 1 *B*) In the left paravertebral region there were soft tissue

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Fig. 1. A. Posterior anterior chest radiograph. Note the nod lar left paravertebral opacity (arrow) which is the dilated hemiazygos vein. The heart is quite large, not characteristic of most patients ith the obstructed form of anomalous pulmonary venous return. The superior vena cava is very prominent. B. Lateral chest radiograph. The reticulated appearance of the lung due to pulmonary venous obstruction is demonstrated more clearly in this view

opacities later demonstrated to represent enlargement of the hemi-azygos vein. (Fig. 1 A)

Laboratory findings. Laboratory findings were as follows: Hg 12 Gm. per cent, W.B.C. 16,700 (S.A. hemoglobin). A repeat cardiac catheterization on May 8, 1969 is summarized in T ble 1. The data were interpreted as follows

1. Left-to-right shunts were present in the right trium, superior vena cava, and inferior vena cava.
2. A right-to-left shunt was suggested by systemic arterial desaturation.
3. Stenosis at the superior vena caval–right atrial junction was demonstrated by occurrence of pressure gradient t this level.
4. Marked pulmonary hypertension was demonstrated to be secondary to pulmonary venous obstruction, documented by wedge pressure of 25 to 30 mm. Hg.
5. A patent ductus was demonstrated by direct passage of the catheter
6. A Interatrial communication was present.

Multiple injections of contrast medium (sodium, meglumine diatrizoates)* were interpreted as follows

1. The right superior pulmonary vein drained into the superior vena cava just above the stenotic ring but below the azygos vein. Contrast material injected in the pulmonary vein or in the dilated hemi-azygos vein (Fig. 2A) traveled retrograde through the hemi-azygos veins, finally entering the inferior vena cav at multiple levels, extending down as far as the right common iliac vein. (Fig. 2B)
2. I jections of contrast into the pulmonary artery demonstrated reversal of flow through the patent ductus nd drainage of the remaining pulmonary veins into the right atri m.

When the child remained in cardiac failure despite rigorous medical therapy surgical intervention became necessary. At surgery the pulmonary veins from the left lung and right lower lobe were found to enter small obstructed chamber behind the right trium. A small patent foramen ovale constituted the interatrial communication. The accessory chamber was opened and sutured to the left atrium. The right superior pulmonary vein was channeled into the left trium by means of a baffle of pericardium which was sutured to the trial septum. The atrial septum was shifted to obtain enlargement of the left trium. The obstruction in the vena cava was enlarged with pericardial graft. The patent ductus was not ligated because of the severe pulmonary hypertension.

Postoperatively the child did well. His liver became smaller, his appetite improved, and the signs of cardiac failure abated.

Discussion

Total anomalous pulmonary venous return may be of the supradiaphragmatic or nfradiaphragmatic type. In the latter pulmonary venous obstruction is almost invariably present, and a characteristic radiographic picture has been described.[1] The findings nclude normal heart size and a reticulated appearance of the lungs

*Renografin, E. R. Squibb & Sons, New York, N. Y.

Table I A. H. cardiac catheterization data May 18 1969

Catheter position	*O_2 saturation %*	*Pressures mm Hg*
Jugular vein	49	
Right subclavian vein	57	
Superior vena cava	73	20/12
Left innominate vein	57	20/12
Right superior pulmonary vein	96	
Right atrium		
a. High	85	a = 6
b. Mid	65	v = 2
c. Low	69	Mean = 3
Inferior vena cava		
a. Mid liver	70 68	
b. Below renal vein	? 63	
c. Left common iliac vein	48	
Right ventricle		
a. High	73	
b. Low	70	90/ 0 6
Main pulmonary artery	67	90/39 mean = 65
Left pulmonary artery	70	90/39 wedge 30/25 mean = 20-25
Descending aorta	63	75/50 mean = 60
Right femoral artery with air	65-69	85/50 mean = 65
Right femoral artery with 100% O	89	

thought to result from interstitial edema secondary to pulmonary venous obstruction. Similar radiographic findings may occur whenever there is obstruction to pulmonary venous flow as in cor triatriatum,[2] the hypoplastic left heart syndrome,[3] or in the obstructed form of supradiaphragmatic anomalous pulmonary venous return.[4]

The obstruction in anomalous pulmonary venous drainage may occur in various locations.[4,6] In the infradiaphragmatic type in which pulmonary venous drainage terminates in the portal system obstruction is due to resistance created by obligatory flow through the hepatic sinusoids. In the supradiaphragmatic type stenosis of the common pulmonary venous trunk of the vertical vein (left superior vena cava) may occur. A very unusual form of obstruction occurs when all four pulmonary veins end in a blind trunk; drainage may then occur through an anomalous vein which leads from the chamber to terminate above or below the diaphragm (Patients 4 and 6 as described by Hastreiter and coworkers[4])

Two sites of pulmonary venous obstruction were present in this patient. Veins from the left lung and right lower lobe of the right lung entered a chamber behind the right atrium which at surgery was found to have only a minute communication with the right atrium. The second site of obstruction in the superior vena cava just below the azygos vein affected the right superior pulmonary vein which drained into the superior vena cava above the stenotic area. Flow then proceeded in retrograde fashion from superior vena cava through left innominate and hemiazygos veins to communicate via the azygos with the inferior vena cava at multiple levels. Thus a portion of the pulmonary venous drainage while anatomically of the supradiaphragmatic type emptied into the inferior vena cava and became physiologically infradiaphragmatic. This collateral pathway of flow is characteristic of superior vena caval obstruction which occurs below the entrance of the azygos vein. Resulting dilatation of the hemiazygos vein produces an irregular left paravertebral opacity on x-ray. The radiographic features of this collateral flow phenomenon previously described by Steinberg[7] may allow clinical diagnosis if properly interpreted.



Fig. 2A Angiogram. Injection into the hemi-azygos vein. The catheter has traversed the narrowed superior vena caval orifice and left innominate vein. Note contrast material passing caudally below the diaphragm. Contrast injected into the right superior pulmonary vein followed similar pathway after first emptying into the superior vena cava above the stenosis.



Fig. 2B Approximately 2 sec. after injection, the contrast can be seen entering the right common iliac vein and the inferior vena cava at several levels.

Summary

A unique case of total anomalous pulmonary venous return in a 22 month-old child is described. Although all veins terminated anatomically above the diaphragm, stenosis at the superior vena caval-right atrial junction forced blood from the right superior pulmonary vein to travel with superior vena caval blood in a circuitous retrograde pathway through the hemi-azygos and azygos veins into the inferior vena cava. The dilated, tortuous hemi-azygos vein produced a left paravertebral radiographic opacity which should prove useful in clinical recognition of this unusual anomaly.

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Clinical pathologic conference

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Case history

First admission (January 1967) This 39-year-old woman wa admitted for complaints of shortness of breath and light headedness. Approx mately nine month before admission she developed dyspnea with moderate exertion and three months later he had the first of many episodes of light headedness. Four month before adm ssion she had an episode of tachycardia which responded to digitalis. The patient denied having chest pain nocturnal dyspnea orthopnea or edema

At one year of age the p tient was found to have a heart murmur which wa attributed to rheumatic fever At age 18 during an employment physical examination the murmur was again noted, and he was advised to restrict her activities and to avoid pregnancy Both in tructions were followed diligently Approximately fifteen years before this admission chest x rays had shown enlarged pulmonary arteries. An appendectomy was performed t age 20 and an abdominal abscess drained nine month later The patient had a history of peptic ulcer disease wh ch responded to antacid therapy She had been tak g birth control pills for several years, but stopped fourteen months before this admission when an intrauterine device was inserted

Physical examination revealed an agitated well-developed woman with a blood pressure of 140/80 mm. Hg in both arms, a regula pulse of 90 per minute, a respiratory rate of 16 per minute and oral temperature of 98 8° F The point of maximum impulse (PMI) was in the fifth i tercostal space at the anterior axillary l ne There wa palpable heave alo g the left lower sternal edge. An ejection click was heard over the second left intercostal space and a grade 2/6 systolic jection murmur was present over the same area A grade 1 2/6 early decrescendo diastolic murmur was present at th third and fourth left intercostal spaces along the left sternal border All pulses were present, equal bilaterally and not delayed There was slight cyanosis, but no cl bbing of the fingers or toes. No other significant findings were noted The hemoglobin was 16 4 Gm per cent hematocrit 48 per cent, and white blood cell count (WBC) 7 800 per cubic millimeter with a normal differential The blood urea nitrogen (BUN) wa 12 mg per cent creatinine 1 0 mg per cent b lirubin, 0.4 mg per cent alkaline phosphatase 5 4 U and uric acid 5.2 mg per cent. Serum glutamic oxalacetic transaminase (SGOT) serum glutamic pyruvic transaminase (SGPT) and lactic dehydrogenase (LDH) were within normal limits. Bromsulphalein (BSP) retention was 18 per cent in 45 minutes. Urinalysis showed large amounts of protein, 4 to 12 WBC per high power field, a pH of 6.5 and a specific gravity of 1 018. Protein-bound iodine (PBI) was 4 9 µg per cent and T_3 resin uptake was 29 per cent. The VDRL report was negative.

On the third hospital day right heart catheterization and selective angiocardiography were performed Within 24 hours the patient s temperature rose to 104 F and she was found to have a rapid irregular pulse She was given intravenous Cedilanid and ubsequently reverted to normal sinus rhythm. She continued to have rectal temperatures of 101 to 102° F Adm nistration of erythromycin was begun. Because of the history of fever and chills following insertion of the intrauterine device (IUD) 14 months previously it was removed The rectal temperatures dropped to levels of 99 to 100° F over the next three days, only to rise again to previous levels. Multiple blood and urine cultures showed no growth sputum cultures yielded normal flora. On the thirty-second hospital day she was tarted on 15 million units of i travenous penicill n per 24 hours. After eight days on this regimen there was no improvement and it was disconti ued Warfarin dosage was begu Within six days the patient became afebrile and remained so to the time of discharge Warfarin was continued.

Interim admissions The patient was admitted a year l ter with complaints of heavy menstrual period dilatatio nd curett ge revealed prolif

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erative endometrium. She was readmitted in July 1968, when hysterectomy and bilateral salpingo-oophorectomy were performed.

Last admission (April 1969) Exertional dyspnea began a few weeks after the last discharge. During the two months prior to this admission, the dyspnea became worse and was accompanied by progressive increase in abdominal girth and edema of the legs. Physical examination revealed a blood pressure of 155/90 mm. Hg in the left arm and 145/90 mm. Hg in the right arm, an irregular pulse of 110 per minute, and a respiratory rate of 22 per minute. There was cyanosis of the lips and nailbeds, and the jugular veins were distended to the angles of the jaws at 45 degree elevation. The PMI was outside the midclavicular line, and there was a prominent left parasternal heave, but no thrill. S_1 was normal, S_2 was narrowly split, and P was increased. A grade 3/6 blowing early diastolic murmur was present along the upper left sternal border. There was evidence of ascites and edema of both legs. The liver was tender and extended 5 cm. below the right costal margin. Hemoglobin was 15.4 Gm. per cent, hematocrit was 52 per cent, and WBC was 6,400 per cubic millimeter with 49 per cent polymorphonuclear leukocytes, 1 per cent basophils, 40 per cent lymphocytes, and 9 per cent monocytes. Urinalysis revealed a pH of 6.5, a specific gravity of 1.011, large amounts of protein, and over 30 hyaline casts per high-power field. Serum sodium was 140, potassium 4.2, chloride 95, and CO_2 content 29.4 mEq. per liter. The BUN was 23 mg. per cent, creatinine 1.2 mg. per cent, SGOT 47 U, SGPT 33 U, LDH 876 U. Total bilirubin was 0.6 mg. per cent with 0.3 mg. per cent conjugated. Arterial blood gas analysis showed a pH of 7.20, P_{O_2} 30, P_{CO_2} 30, oxygen saturation, 24 per cent. Oxygen administration resulted in some improvement of the tachypnea, but the cyanosis persisted.

On the second hospital day *crepitant râles* were heard in both lung bases, the rectal temperature was 101 F, and increased muscle tonus and hyperreflexia were noted in the left arm and left leg. Oxygen, aminophylline, hydrocortisone, and tetracycline were given with poor response. Fifty hours after admission the patient became apneic and comatose, requiring artificial ventilation. She was unresponsive to pain and had clonic contractions of the left extremities and left side of the face. Dilantin and V-Kum were given with some improvement. Late in the evening of the third hospital day the patient became conscious and was able to speak. There was no spontaneous motion of the left extremities, and no morbid resistance was encountered. The pupils were equal in diameter and both reacted to light. Left facial weakness and sustained left ankle clonus were demonstrable. A questionable Babinski sign was present on the left side. Cerebrospinal fluid pressure was normal; the fluid was clear and colorless with 20 mg. per cent protein, 170 mg. per cent glucose, and no cells. Blood sugar obtained simultaneously was 312 mg. per cent.

On the fourth hospital day the patient was more alert and started feeding herself, but she had short episodes of confusion. She remained febrile. Hemoglobin was 15.6 Gm. per cent and WBC was 21,900 per cubic millimeter with 95 per cent polymorphonuclear leukocytes, 4 per cent nonsegmented neutrophils, and 2 per cent monocytes. Blood cultures were negative, and sputum cultures showed normal flora. Tetracycline was discontinued and intravenous cephalothin was begun. On the seventh hospital day cardiorespiratory arrest occurred and resuscitation was unsuccessful. *Just before she died it was noted* that the lower extremities were more cyanotic than the upper extremities and face.

Discussion

DR. SILBER:* I think that it is not difficult, in reviewing the protocol, to reduce the diagnosis to the *family of disorders to* which this case apparently belongs. I am referring to the Eisenmenger syndrome, a condition which is much discussed in the literature, but which is still relatively infrequent when we consider the number of fully authenticated cases. The term designates a situation in which, on the basis of congenital heart disease, a large communication exists between the pulmonary and systemic circulations in association with progressively increasing high resistance in the pulmonary circuit. I stress *an association with* rather than because of the large communication inasmuch as the burden of evidence certainly seems to indicate that the high resistance is not necessarily etiologically related to the size of the defect. As a matter of fact it would be difficult to specify why some patients with large arteriovenous communications between the pulmonary and systemic circulations develop this high resistance and others do not, but I will defer any discussion of that to a little later in the meeting.

It seems clear that this patient, *a woman* of about 40, is in serious trouble in her fifth decade of life—a situation quite characteristic of a patient with Eisenmenger syndrome. In the Eisenmenger syndrome the communication may be at the atrial level, at the ventricular level, or at the extracardiac level between the pulmonary artery and the aorta. As a matter of fact, the concept of Eisenmenger syndrome can be extended even beyond that to less common lesions such as truncus arteriosus, some forms of transposition of the great vessels, and so on. But for a

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patient to survive to the age of 40 it would be a foregone conclusion that one of the three common lesions will be found as the basis for Eisenmenger syndrome

The Eisenmenger syndrome is an extremely interesting lesion from the conceptual view of congenital heart disease because it is from this type of case that students of congenital heart disease have come to realize that an understanding of congenital heart disease involves more than just defining anatomical entities Such cases teach that the clinical picture and natural history of congenital heart disease are determined not so much by the fixed anatomic entity as by the varying pathophysiology that evolves during the course of the disease Nothing illustrates this better than the evolution of physiology that occurs in the Eisenmenger syndrome a subject which will be touched upon by Dr Shaffer and myself Moreover I am sure the pathologist will show some remarkable slides of the pulmonary circulation which is so dramatically altered in Eisenmenger syndrome

To return to the case at hand here is a patient who at the age of one year was known to have a murmur which of necessity points to some form of congenital heart disease It is remarkable that someone attributed it at that age to rheumatic fever a disease with which we need not be concerned The patient had enlarged pulmonary arteries tended to have episodes of rather nonspecific light headedness without loss of consciousness became increasingly dyspneic through the years (as one would expect) and ultimately developed right heart failure The murmurs were rather nondescript or atypical and fitted the usual case of Eisenmenger syndrome in that there was an ejection type murmur during systole The diastolic murmur both in character and location was consistent with pulmonary insufficiency which is usual in Eisenmenger syndrome There was also evidence of pulmonary hypertension inasmuch as there was a closely split second sound with accentuation of the pulmonary component a right ventricular lift and a relatively quiet precordium I believe that the electrocardiogram (ECG) and the x rays will be helpful in this regard

Ultimately in her thirties, the patient developed cyanosis which was persistent, and from the time-course alone it is quite easy to pinpoint the cause of the cyanosis. Cyanosis appearing in young adults who were not previously cyanotic (so-called cyanosis tardive) almost invariably indicates congenital heart disease of the Eisenmenger type Cyanosis on a pulmonary basis usually occurs much later in life, whereas patients who have cyanotic heart disease with an obligatory right-to-left shunt are cyanotic from birth Consequently this patient fits very well into the Eisenmenger syndrome

Ultimately the patient died with signs of hypercapnea which was evidence of hypoventilation whether this hypoventilation was central or on the basis of ventilation of unperfused alveoli I will not go into it the moment. It is obvious that she developed a typical acidotic hypercapneic picture ultimately affecting her sensorium. When given assisted respiration the patient regained consciousness but died abruptly with right heart failure and the varying neurologic phenomena which are common in such patients

In order to be able to say whether this patient had Eisenmenger syndrome on the basis of atrial septal defect, ventricular septal defect or patent ductus the x rays will be very helpful the electrocardiograms perhaps somewhat less so but still important. Of course the final sentence of the protocol which states that the patient terminally was noted to have cyanosis that was more marked in the lower extremities than the upper extremities, certainly invites one to suggest that the shunt is evidently at the level of the ductus. The case at once then becomes an instance of patent ductus with reversed shunt due to progressive pulmonary hypertension In other words the Eisenmenger syndrome with extracardiac communication between the systemic and pulmonary circulations. That is my diagnosis and I think that we should see if it will be substantiated by other data

DR LEVIN* I prefer to hear the electro-

*Director Department of Diagnostic Roentgenology Michael Reese Hospital and Medical Center; Professor of Radiology Pritzker School of Medicine, Chicago.



Fig. 1 Chest film of Feb. 1 1967 The heart is moderately enlarged, the pulmonary artery segment is prominent, and the aortic "knob" is small. The hilar and peripheral pulmonary vascular shadows are quite prominent.

Fig. 2 Chest, July 17 1968. No evident change since February 1967

cardiographer present his findings first because I need all the help I can get. The first chest film we have of this patient is in February 1967 (Fig 1) the last in July 1968 (Fig) approximately ten months before her death In between there were a number of other films, all looki g the same There is moderate cardiomegaly and there is prominence of the pulmonary artery segment and the pulmonary arteries at the hila vascularity is also prominent in the periphery of the lung fields. The chamber involvement is one that I have trouble guessing at here, and often. I am as some of you know rather nihilistic as to whether or not the roentgenologist can really make an accurate assessment as to whether there is right ventricular enlarge ment, left ventricular enlargement or preponderance of one or the other On the lateral view the esophagram shows no evidence of left atrial enlargement. There is some prominence of the heart shadow encroaching on the retrosternal air space which would support (but not indicate) that there is right ventricular enlargement. Therefore putting these two together I would suspect that this 42 year-old lady if she does have an intracardiac shunt is more apt to have an interatrial than an interventricular septal defect since in the latter at her age I would have expected some left atrial enlargement. I would say the same for a patent ductus arteriosus but of course, this need not hold if the shunt is, as Dr Silber suspects a right to-left one of long standing

It has been said by many that if one sees disproportionate vascularity in the proximal and distal lung fields, that is, sharp diminution in vascularity in the peripheral lung fields while there is prominence of the hilar vascular pattern this supposedly reflects pulmonary arterioscle rosis, more favorable for interventricular than for interatrial septal defect. I have indeed seen many cases of interventricular septal defect which present such a picture of the pulmonary vascular pattern, but so have I seen cases of interatrial septal defect as well as patent ductus arteriosus. Likewise, without disporportionate vascu larity between proximal and peripheral lung fields, as in this case a shunt can be intracardiac, at any level or extracardiac. Therefore I think the best that I can offer

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taken in 1967 while the patient was receiving digitalis medication, which accounts for the shortened and depressed ST segments and the small T waves. There is undisturbed sinus rhythm (rate 96) with a normal P R interval (0.16 sec.) and QRS duration (0 08 sec.) The striking features are (1) large, narrow and pointed P waves, upright in Leads II III and aV_F and diphasic in V suggesting right and possibly biatrial enlargement (2) the rsR complexes in V and V with prominent S waves in V consistent with right ventricular hypertrophy and a minor right sided intraventricular conduction defect. In this context the large R waves over the left precordium may indicate concomitant left ventricular hypertrophy This, however is not confirmed by a vectorcardiogram taken at that time (Fig 6) which shows only the terminal conduction delay in right ventricular hypertrophy

Two preterminal arrhythmias observed in the patient are illustrated in Fig 7 On April 17 1969 the configuration of the ventricular complexes has not changed except for a shift of the frontal QRS axis to about +90° The action of atria and ventricles is faster and irregular All ventricular complexes can be related to P waves but not vice versa. The P waves are of variable shape none resembling the sinus P waves of the record of 1967 P R intervals change in an inconsistent and unpredictable manner within range of 0 16 to 0.50 second. On several occasions the P R interval exceeds the P P interval so that two P waves precede a QRS the second one being blocked ("skipped" P waves) Thus, a multifocal ectopic atrial tachycardia with irregular ventricular response was present on this day conceivably engendered by digitalis after acute potassium depletion.

The third record (Fig 7) obtained a day before the patient's death shows return of a fast sinus rhythm (rate 130) with a constant and normal P R interval. In Leads I to III every second sinus beat is followed at a shortened P R distance by a ventricular complex that differs from the dominant beats by a QRS duration of 0 10 sec a larger and slurred RS deflection in Lead I and smaller R waves with

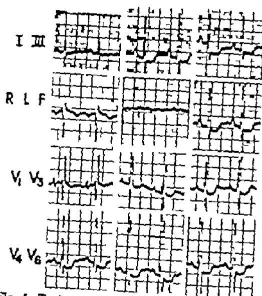


Fig 5 Twelve-lead electrocardiogram taken Feb 23 1967 (described in text).

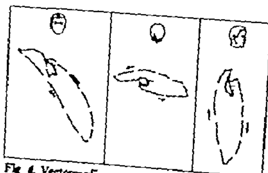


Fig 6. Vectorcardiogram taken Feb. 7 1967 in the frontal, horizontal, and right sagittal planes.

prominent "Q waves" in Leads II and III These beats are open to four different interpretations (1) premature ventricular ectopic beats revealing an otherwise latent posteroinferior wall infarct[1] (2) fusion of a premature ectopic ventricular and a sinus impulse (3) intermittent ventricular pre-excitation (WPW) and (4) A V junctional premature beats with aberrant ventricular conduction. Of these possibilities the first is least likely within the clinical context, the second and third cannot be excluded on the basis of the limb leads, and pre-excitation would be a particularly attractive diagnosis in the presence of the clinically suspected congenital malformation However the fourth diagnosis, that of junctional premature beats with aberrant ventricular conduction can be es-

Fig 3





Fig

Fig 3 Angiocardiogram Enlarged pulmonary arteries are evident. There is a localized area of diminished opacification of the right pulmonary artery *(just to the right of the spine)*

Fig 4 Angiocardiogram venous phase. There is no evidence of intra or extracardiac shunt.

is that there is cardiomegaly and a pulmonary vascular pattern that I think reflects a left to right shunt. Further than that I would not venture to guess That is why I think the electrocardiographer has so much more to offer the ECG is certainly a more sensitive indicator of chamber predominance than are films in a case such as this.

Angiocardiography was performed biplane I will show you only the frontal views (Figs 3 and 4) On this first film the catheter is in the right ventricle there is enlargement of the right ventricular chamber and marked prominence of the pulmonary arteries before and after initial branching One can see further that there is prominent vascularity into both lung fields with normal distribution of the arterial supply The arteries are wide and tortuous all the way out to the periphery There is no evidence of left atrial enlargement In the right pulmonary artery projected just to the right of the vertebral column there is a length of a few centimeters that is less opaque than the adjacent contrast-containing artery proximal or distal to it. Also the lumen seems rather abruptly and moderately narrowed This appears to be caused by an annular defect in that pulmonary artery probably a thrombus causing a low-grade obstruction

The angiocardiogram gives no support to the left to-right shunt which I suspected to be present from the plain film findings. At no time in the course of the study could we see early filling of the aorta to indicate filling from the pulmonary artery directly nor is there any other evidence of a right to-left shunt

DR KABINS* Could you demonstrate pulmonary insufficiency?

DR LEVIN No

DR. KABINS Dr Silber does the lack of demonstrable pulmonary insufficiency on angiocardiogram disturb you?

DR SILBER No I think that this is no more surprising than the data that Dr Shaffer will present.

DR. SHAFFER I have a comment. On a right ventriculogram you would not expect to be able to demonstrate pulmonary insufficiency since you are injecting into the ventricle and would not see a reflux back.

DR. PICK† Of the many electrocardiograms that were obtained during and between the several hospital admissions I selected three representative ones and one vectorcardiogram The first (Fig 5) was

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unusual course. The blood pressure and oxygen data are shown in Table I.

Mean right atrial pressure is normal while right ventricular end-diastolic pressure is at the upper limit of normal. The discrepancy between these pressures is due to an augmented wave of atrial systole. This reflects the transport function of the atrium[2] which is made particularly evident when there is a markedly increased systolic overload of the ventricle. Forceful atrial systole distends the ventricle to the fullest at end-diastole but because atrial systole is short this pressure rise is reflected very little in mean atrial and central venous pressures.

Pulmonary artery pressure is elevated to systemic levels as is right ventricular systolic pressure. There is no systolic pressure gradient across the pulmonary valve. Simultaneously recorded pulmonary and brachial artery pressures are virtually identical. The breathing of oxygen in high concentration did not significantly affect this relationship. Pulmonary artery wedge pressure which would represent left atrial pressure could not be obtained. This is not unusual in severe pulmonary hypertension. I would expect this pressure to be in the normal range of 3 to 10 mm. Hg.

Except possibly for the single high figure of 14.2 vol. per cent in the right pulmonary artery, the oxygen contents of a series of blood samples obtained from the lesser circulation do not suggest left-to-right shunting of blood. On the other hand, a brachial arterial blood oxygen saturation of 85 per cent strongly suggests a right-to-left shunt. During the breathing of oxygen in high concentration arterial blood oxygen saturation rose to only 97 per cent, which would further indicate that desaturation is on the basis of a circulatory right-to-left shunt rather than on a pulmonary parenchymal basis.

On the assumption that the blood oxygen data reflect shunting of blood in *both* directions, the relative sizes of the shunts and the ratios of blood flows and vascular resistances in the systemic and pulmonary circulations can be calculated. Thus, a left-to-right shunt, if present, is very small, making up 10 per cent of pulmonary flow. The right-to-left shunt makes up about 26 per cent of systemic flow. The

Table I. Catheterization data

Catheter location	*Blood oxygen content (vols %)*	*Blood pressure syst./diast. (mm. Hg)*
Inferior vena cava	12.0	
Superior vena cava	13.3	
Right atrium		
High	12.1	
Mid	12.4	(3)
Low	13.3	
Right ventricle		
High	12.2	145/8
Low	12.2	
Apex	12.4	
Main pulmonary artery	11.5	
	13.4	
Right pulmonary artery		150/75 (93)
	14.2	145/73 (96)†
	15.9‡	144/70 (94)‡
Left pulmonary artery	13.6	150/75 (97)
Brachial artery		
Content	18.9 21.2‡	145/78 (95)†
Capacity	20.5 21.8	138/70 (90)‡
Saturation	85% 97%	

*Numbers in parentheses = means.
†Simultaneous.
‡Simultaneous, high oxygen breathing.

ratio of pulmonary flow to systemic flow is 0.83 and the ratio of pulmonary to systemic resistance is 1.1, which is exceedingly high, pulmonary resistance actually exceeding systemic.

Fig. 8 shows four of the many indicator-dilution curves obtained in the course of this catheterization study. The two curves on the left were obtained by *injection* of indicator into the right side of the circulation with sampling in the left side. The lack of a double peak and of a short appearance time in the lower curve virtually excludes right-to-left shunt at any usual site. This finding was unexpected and not a little mysterious. It could be argued that if there were a patent ductus arteriosus with right-to-left shunt, it could be missed by brachial artery sampling since venous blood passing through the ductus is primarily directed into the descending aorta. The shunt would thus be more likely detected by femoral arterial sampling. This however does not explain the dye curve

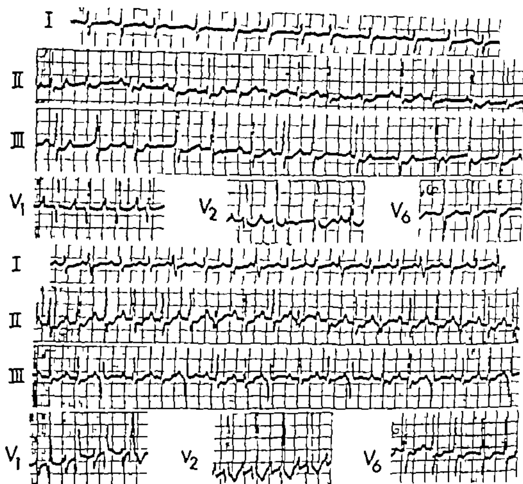


Fig 7 The preterminal arrhythmias (described in text) *A* Taken April 17 1969 *B* taken April 20, 1969

tablished with the help of Lead V_1 since here the premature (fourth) beat resembles the sinus beats except for a larger R and a (secondary) inversion of the T wave without a demonstrable delta wave

To summarize the electrocardiographic findings I cannot state whether the marked right ventricular hypertrophy is congenital in origin or acquired Additional left ventricular hypertrophy may or may not be present I also would expect atrial disease with enlargement of mainly the right atrium As far as a specific diagnosis is concerned this could be an atrial or ventricular septal defect or a patent ductus with pulmonary hypertension in short any of the known types of the Eisenmenger syndrome

DR SILBER The ECG is what one would anticipate. Whether or not there is combined ventricular hypertrophy there certainly is evidence of right ventricular hypertrophy Had we not seen that we would have had to turn in a direction different from the Eisenmenger syndrome Some of the other findings are a little disappointing and perhaps part of the limitation of the technique

As far as the x rays are concerned they are consistent with what is happening hemodynamically during the course of the patient s illness. The heart size shown on the x ray suggests that if this were an atrial septal defect there never was at any time any sizable shunt and that almost from birth the resistance was quite high and remained high By and large with large shunts at the atrial level associated with such large pulmonary arteries, one would anticipate a larger heart size The minimally enlarged heart without clear-cut chamber enlargement on the left side either atrial or ventricular does not help to differentiate between patent ductus and ventricular septal defect but strongly rules against atrial septal defect

At this point Dr Shaffer will you discuss the catheterization data?

DR SHAFFER* The catheter took no

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eterization is really very slim and I say that based upon two considerations. If bacterial endocarditis had occurred and the evidence of it was so immediate as in this case, a very virulent organism would have had to underlie the infection. The patient then would have been extremely ill and have shown clinical features that we associate with such virulent organisms which are so highly destructive of the valve or other sites in which they are located. On the other hand if this was an organism of low virulence the viridans type, we should not have anticipated that fever and signs of infection would have appeared so rapidly.

DR. KARDOS What if there was pre-existing endocarditis with low-grade or no fever? Could cardiac catheterization and angiographic studies stir things up?

DR. SILBER Well I think that is quite remote. I won't say that it could not happen, but frankly I think otherwise. The other point I was going to make as to the reasons I don't think bacterial endocarditis was responsible for the fever is the fact that in a cooperative study that was done by many major institutions around the country involved with cardiac catheterization the incidence of endocarditis following catheterization was of an exceedingly low order only a fraction of 1 per cent. Therefore, it would seem that this hazard is very very low. Moreover the patient responded favorably to anticoagulants, which are ordinarily disastrous in the treatment of bacterial endocarditis. I might, therefore, postulate another basis for the fever. We know that in the Eisenmenger syndrome the changes in the small pulmonary arteries and arterioles are really very striking. They follow a certain pattern first described by Edwards and associates[4] and Civin and Edwards. One of the final stages which is rarely seen may be an arteritis. While it is not seen commonly in the Eisenmenger syndrome it may occur. One is invited to suggest that perhaps there was such a necrotizing arteritis, possibly on a hypersensitivity basis. It is possible that there might have been some untoward reaction to the dye. Perhaps the patient was sensitive to it or the dye induced some sort of insult to the pulmonary vascular tree that resulted in an arteritis associated with fever. However I would not be able to answer why this should clear up with anticoagulants even though I am aware that thrombi in situ and perhaps propagated thrombi from larger arteries into smaller arteries may be part of phases that we see in the pulmonary circulation during the natural history of the Eisenmenger syndrome. Perhaps in some way the administration of anticoagulants was effective in this aspect of the case. This is pure speculation. I am more secure that endocarditis was not present than being able to give a precise reason as to why the fever responded to the anticoagulant.

That this patient went progressively downhill and demonstrated right heart failure is to be anticipated. This is the manner of death in these patients. With the stupor of pulmonary insufficiency due to hypoventilation and the subsequent neurological abnormalities, one could speculate that one of two things may be found. Although she did not have remarkable polycythemia it is possible that this patient experienced thrombi in the central nervous system which formed on the basis of right heart failure, the low cardiac output, and the relatively high hemoglobin. Alternatively the neurologic picture may simply have been a manifestation of the severe hypoxia that was present during this situation. Obviously it was at least in part reversible. The patient died abruptly without clear evidence as to whether death was due to a disorder of rhythm or was respiratory and this is the typical way that patients with Eisenmenger syndrome die.

Normally when a person is born there is a dramatic change from a placental circulation to a pulmonary circulation for ventilation and this is ordinarily associated with a marked drop in pulmonary vascular resistance. Should this marked vascular resistance remain of the same order as it is in fetal life, the stage is set for what is called the Eisenmenger syndrome. Civin and Edwards originally explained the persistence of the high resistance in the pulmonary circuit on a teleological basis, namely that if there were not a high pulmonary resistance in the face of a large communication at the atrial ventricular or aorticopulmonary level the patient

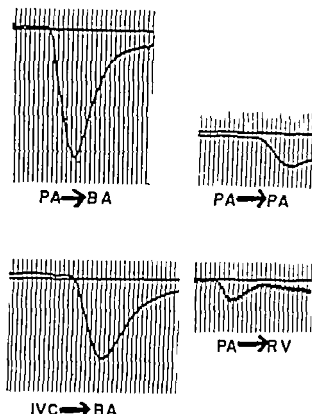


Fig 8 Indicator dilution curves, each labelled as to site of injection and sampling abbreviations as in Table I Time along the horizontal axis distance between vertical lines represents one second. The left edge of each figure marks the time of injection of indicator Downward deflection of curve reflects increasing concentration of indicator

findings since the upper extremities were cyanotic brachial arterial blood was desaturated and the right ventriculogram failed to show early opacification of the descending aorta

The two curves on the right of Fig 8 were obtained by both injection and sampling of tracer on the right side of the circulation The upper curve is due to injection in one pulmonary artery with sampling in the contralateral one This curve excludes virtually any left to-right shunt which if present would have resulted in a shortened appearance time due to an additional early peak This curve was repeated after high oxygen breathing and still showed no evidence of left to-right shunt. The right lower curve has the appearance of a left to-right shunt but in this case actually represents pulmonary valve insufficiency since shunting was excluded by the previous curve

So in conclusion we decided that this was a case of Eisenmenger syndrome with particularly severe pulmonary vascular obstruction and *pulmonary* valve insufficiency in which we failed to demonstrate exactly where the abnormal communication was. This could be due to a balance of systemic and pulmonary resistances such that there was no shunt occurring at the time of the study and certainly any left to-right shunt was excluded quite definitely the other possibility is that for some mechanical reason the shunt was temporarily or permanently cut off in which case we would have to "alibi" the cyanosis on a pulmonary parenchymal basis

DR SILBER I think the evidence for an Eisenmenger syndrome is complete in the sense that the clinical features are consistent with the data of catheterization, namely that central cyanosis is associated with systemic and pulmonary resistances which are virtually the same. I think that, although Dr Shaffer is disappointed about the failure to show it with the dye technique he would accept the existence of a right to-left shunt as I would because of the failure to be able to improve the arterial saturation with 100 per cent oxygen breathing Obviously the shunt is small and occurring during some phase of diastole. With neither an atrial septal defect nor ventricular septal defect the Eisenmenger syndrome would exhibit lower extremities which are more cyanotic than the upper extremities. On the other hand the insertion of a ductus from the left pulmonary artery to the aorta is such that venous blood is diverted to lower rather than the upper aorta Therefore, I am satisfied that the Eisenmenger syndrome was on the basis of a reversed ductus Sometimes the left subclavian receives the blood and the left arm may be more cyanotic than the right This was not present but it is not a necessary finding

There are some other things that require discussing One of them of course is the fever that developed after catheterization. Despite the fact that cultures were negative it was evident from reading the protocol that the patient was treated as if bacterial endocarditis were present. However I believe the chance of bacterial endocarditis being present r the cath

scopically there was diffuse neuronal degeneration which was most pronounced in the cerebral and cerebellar cortices. In some areas there was actual loss of neurons as well as degenerative changes. No thrombi were observed. The liver showed severe congestion with mild fatty vacuolization and the kidneys exhibited mild acute tubular necrosis as well as congestion.

The heart was quite large, considering the patient's weight of 100 pounds. It weighed 440 grams. The enlargement was due primarily to right ventricular hypertrophy, the right ventricular wall measuring 0.8 cm. in thickness, and to a lesser degree to left ventricular dilatation and mild hypertrophy, the left ventricular wall measuring 1.2 cm. in thickness. The cardiac valves showed no significant abnormalities. The atrial and ventricular septa were intact, and the foramen ovale was anatomically closed. The shunt was located at the level of the ductus arteriosus which was widely patent, measuring 1.3 cm. in length and 1 cm. in diameter (Fig. 9).

The pulmonary trunk, particularly around the orifice of the ductus, and the main pulmonary arteries were dilated and showed severe atherosclerosis. The right pulmonary artery was completely occluded by a thrombus (Fig. 9). Portions of the thrombus appeared rather old, with complete organization and recanalization; others were more recent and only partially organized. The thrombotic process probably began a number of years before the patient's death and undoubtedly accounts for the right pulmonary artery abnormality demonstrated by angiocardiography during the patient's first admission.

The lung parenchyma was normal both grossly and microscopically, but the pulmonary vascular tree showed severe and extensive changes associated with the hypertension. The large elastic arteries of the lung exhibited severe atherosclerosis with marked eccentric thickening of the intima. The most striking changes, and probably of most importance functionally, however, were those affecting the small muscular arteries and arterioles. These vessels were markedly thickened due to medial muscular hypertrophy and varying degrees of



Fig. 9. Gross picture showing marked hypertrophy of right ventricular outflow tract, dilated pulmonic valve, dilated and therosclerotic pulmonary trunk, patent ductus arteriosus (probe), and thrombotic occlusion of right pulmonary artery orifice.

fibrous proliferation of the intima. In some vessels this had progressed to complete obliteration of the lumen by concentric layers of collagen and elastic fibers (Fig. 10). Frank necrotizing arteritis was not present in this case, but several vessels showed disruption of the media by what appeared to be granulation tissue, possibly representing arteritis in a healing stage.

The lesion which is probably of most significance in contributing to the elevated pulmonary vascular resistance is the so-called plexiform lesion which consists of a network of small vascular channels located at the small artery and arteriolar levels, just proximal to the alveolar capillary bed (Fig. 11). The pathogenesis of plexiform lesions is not known, although many theories have been proposed; however, there appears to be some correlation between the number of these structures present and the degree of shunt reversal.

One final significant finding was the abnormal elastic tissue pattern of the pulmonary trunk. The number and arrangement of the elastic fibers in this case was

would be unable to sustain a normal systemic cardiac output and would die in shock. Therefore the high pulmonary vascular resistance compensates and permits the patient to have a normal cardiac output. Unfortunately this relationship is not confirmed because many times patients who require such a high pulmonary vascular resistance for survival, for example the so-called malignant ductus, do not develop it and die. Conversely, patients who have no need of such high pulmonary vascular resistance, for example an occasional case of pulmonic stenosis with intact ventricular septum or an uncomplicated coarctation of the aorta, are also found to have high pulmonary vascular resistances and pulmonary hypertension which serve no purpose. Thus at present no one knows what the stimulus is to the pulmonary vascular resistance remaining high in these cases and no one knows why it drops in other cases. Actually, it has not been excluded that these changes are simply an expression of an anomaly of the entire pulmonary vascular tree that is present in conjunction with some of these anomalies and absent in others or that there is some genetic hypersensitivity present in these patients as compared to others. That there might be such difference in sensitivity is suggested by the fact that when one studies various species, for example lambs versus calves, as to the effect of hypoxia of high altitude on the pulmonary pressure of these animals born at such altitudes, one finds that calves are extremely sensitive and have very high pressures, whereas the lamb is relatively insensitive to the hypoxia of high altitude and does not develop much pulmonary vasoconstriction at all.

DR. KABINS. Do you believe that the patient, at the time she was first seen and evaluated, was beyond the stage where cardiac surgery would help?

DR. SILBER. It is hard to say, but it would seem to me that since this patient had a high pulmonary vascular resistance almost approaching systemic levels from the time that she was seen, and since her murmurs were already the attenuated murmurs that we find in so-called atypical ductus indicating that the left-to-right shunt is already very small, chances are that such a patient would not have done well with surgery.

DR. PIPER. I have two questions. Was the patient put on anticoagulants during the last admission, and is there a possibility of an embolic phenomenon, possibly a paradoxic embolus to the brain, to account for the neurological findings?

DR. GOZO. Anticoagulants were continued throughout her course.

DR. SILBER. I don't think the chance of a paradoxic embolus through a patent ductus is very great. But the question would arise in the presence of right heart failure whether one could have paradoxical embolism through a patent foramen ovale that might open during the stage of right heart failure terminally. We can only acknowledge that such would remain a possibility. We would also have to assume that the patient's emboli were coming, as they do in other garden varieties of right heart failure, from the abdominal and extremity veins rather than having anything to do with the pulmonary circuit.

DR. CHRIST.* Before describing the cardiovascular and pulmonary pathology, I would like to present the findings related to the terminal features of the patient's course. A completely unexpected finding, but one which certainly accounts for the terminal fever and leukocytosis and possibly the elevated serum glucose level, was severe and extensive acute pancreatitis. This was associated with extensive parenchymal necrosis and neutrophilic infiltration with the formation of microabscesses. There is no good explanation for the presence of pancreatitis in this case. The conditions most commonly associated with this condition—liver disease, biliary disease, and alcoholism—were not present and we are left with the possibility that it resulted from severe congestion and hypoxia. Pancreatitis is an unusual but a recognized complication of severe right heart failure.

The neurological manifestations were due to anoxic encephalopathy. The brain showed no grossly apparent lesions such as hemorrhages or infarcts, but micro-

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Fig. 11. Plexiform structure consisting of complex network of thin-walled vascular channels. Cellular area at right possibly represents small organizing thromboembolus. (Hematoxylin and eosin. ×200.)

DR. SILBER. I think we are committed to the fact that if there was differential cyanosis, there was sufficient difference between the systemic and pulmonary vascular resistances to permit this obvious reversal of shunt. So that I would certainly accept the fact that shock has permitted this differential. To put it the other way around one could say that one of the ways to try to establish the diagnosis of atypical ductus in such a balanced shunt would be to give a pressor drug. It has been reported that when a pressor drug is given which raises the systemic pressure you get a typical to-and-fro ductus murmur rather than the nondescript systolic murmur that is so difficult to interpret. I would certainly say that, again, in either direction this is a manifestation of the fact that congenital heart disease is very much involved with physiology, not merely fixed anatomic lesions. Moreover, the clinical picture and its evolution are expressions of the variation in physiology that is going on in the patient at the time.[4]

As far as commenting on the basis for these pulmonary vascular changes, one could talk at great length but would come back to the fact that little is known about them. They are related to flow, but not entirely, because one cannot relate large flow and high pulmonary pressure in any coherent way. If one goes through the literature, it is evident that high flow does not automatically correlate with high pulmonary pressure. There is a very poor correlation and for that reason it is clear that the changes are not due simply to the high flow. Flow is certainly important and relevant here, but it obviously isn't a one-to-one relationship; there is something more that is involved. If one could understand what are the factors involved in the normal involution of the fetal type of architecture in the first place, and why they persist in some patients and do not in others, perhaps we could get some explanation. There is no question that the extent of the damage, once it does develop, is in some way related to the height of the

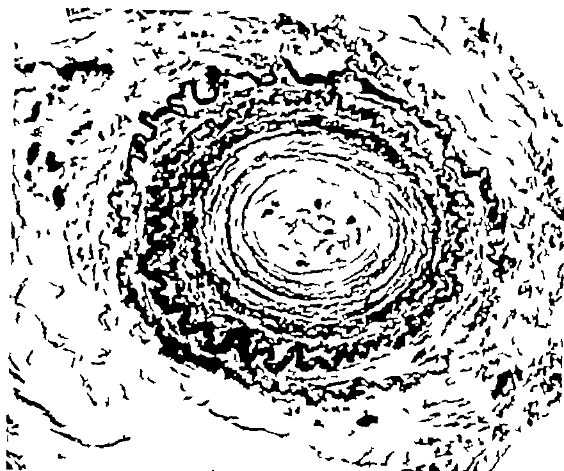


Fig 10 Small muscular pulmonary artery showing mild medial hypertrophy and marked fibroelastosis of intima with almost total occlusion of lumen (Verhoeff van Gieson ×200)

similar to that seen in the normal high pressure aorta and fetal pulmonary trunk. This retention of fetal architecture of the pulmonary trunk is said to occur only in those cases of pulmonary hypertension in which increase in pulmonary flow and/or pressure are present from birth thereby preventing transition to the adult pattern which normally occurs during the first two years after birth In pulmonary hypertension acquired after infancy the pulmonary trunk shows muscular hypertrophy but retains the adult elastic tissue pattern which is characterized by fewer shorter and more loosely arranged fibers [7]

In summary this is a case of Eisenmenger syndrome complicating patent ductus arteriosus and associated with progressive thrombotic occlusion of the right pulmonary artery Severe right heart failure anoxic encephalopathy and acute pancreatitis were terminal events.

DR. PICK Did you find any pathology in the atria grossly or microscopically?

DR. CHRIST Only mild dilatation

DR MILLER* It might be worth while to comment on the actual occurrence just prior to the time of death Basically our thinking was similar to that of Dr Silber's. On the morning of death the patient was in a shocklike state and at that time the observation was made that she had marked cyanosis of the lower extremities and not nearly as much in the upper extremities. The question that came up was why if she had a patent ductus, should that occur at that time? Our explanation was, and I wonder if Dr Silber would comment that there had been a fall in peripheral vascular resistance and that the balance between the systemic and pulmonary pressures had been changed to facilitate a considerable right to-left shunt that had not been present at the time Dr Shaffer catheterized her

DR KABINS Would you also comment on what is known about the pathogenesis of these pulmonary changes.

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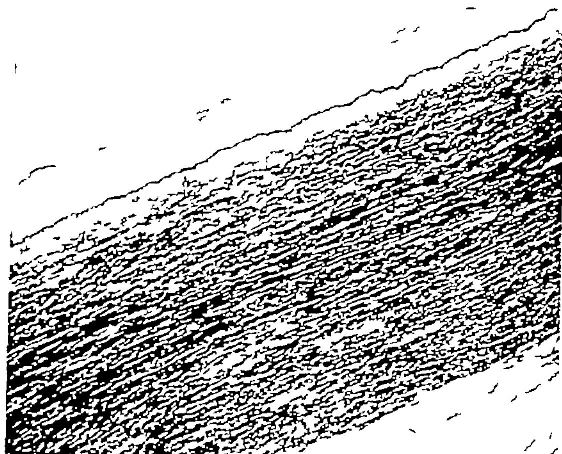


Fig 12 Section of pulmonary trunk exhibiting thickened intima and abundant long elastic fibers arranged in a circumferential and parallel pattern (Verhoeff van Gieson × 40)

pressure It is for that reason therefore that in atrial septal defect these changes occur rather late whereas they occur rather early and are severe in ventricular septal defect and patent ductus It has been suggested recently that one of the reasons for the severe damage in these last two lesions is the manner in which blood at high flow is introduced into the pulmonary circulation There is a marked shearing effect on the endothelium and this shearing effect leads to much more damage than in the case where comparable flows reach the pulmonary circulation via the atrial septal defect. In the Eisenmenger syndrome the pulmonary vascular changes have been described in exquisite detail and their evolution can be predicted but what the initial stimulus is and what is the exact mechanism of their production is still virtually unknown

DR MILLER I would like to ask Dr Christ whether in any of the lesions that you showed particularly some of those that were in transition you can rule out that they were due to pulmonary thrombotic processes at the smaller vessel levels. Specifically in trying to correlate this with the clinical picture whether there might not have been a period of time when the patient did have either pulmonary thromboses or small pulmonary emboli occurring the process of which was altered by the use of anticoagulants

DR CHRIST No I cannot rule out that possibility As a matter of fact, one of the theories regarding the evolution of plexiform lesions is that they result from organization and recanalization of small vessel thromboemboli

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mal tracings presented in this paper were obtained from patients who were fully studied including catheterization and angiography. In addition it should be pointed out that our criteria for the phlebographic diagnosis of tricuspid insufficiency depended ultimately on the verification of our diagnosis at surgery.

The normal jugular pulse

The jugular pulsations are due to interaction of two basic factors: the flow of venous blood toward the heart and the pulsatile activity of the right atrium and ventricle. These two forces are modified by the transmural influence of intrathoracic respiratory pressure oscillations. The designation of various undulations is given in Fig. 1. This is the time-honored nomenclature initiated by Mackenzie (*a*, *c*, *x*, *v* and *y*) to which Hirschfelder[4] and Wood[14]* contributed the remaining two symbols (*h* and *z* respectively).

The a and the a'. The *a* wave is caused by atrial contraction.[11] It is usually assumed that this contraction ceases with the peak of the *a* wave. It has been known, however, since Ewing's[4] experimental studies, that the contraction does not end with the crest of the *a* wave. The crest merely indicates that the contraction has begun to plateau. This maximally contracted state, meanwhile, continues until the *z* point. Then a precipitous transition into the dilatation phase takes place. The effect of atrial contraction is a sudden influx of atrial blood into the ventricle, and a rebound from the ventricular wall. This causes subvalvular eddies, floats the A-V leaflets into apposition, and balloons them toward the atrium. Bard[11] termed this the "intersystolic wave" and labeled it *s*.[11] Ewing documented it experimentally in A-V blocks, inhibition of ventricular contraction (no *c* wave) or with prolongation of the P-R interval (delay in appearance of the *c* wave). With normal A-V conduction this wave is completely obscured by the superimposition of the virtually simultaneous *c* deflection. With prolonged P-R interval, however, it can be recorded, and it then becomes the identifying mark for the *z* point, i.e., the termination of atrial contraction. Ewing[4] named this the *second atrial wave*, and thus led us to mark it with the symbol *a'* (Fig. 2).

The c. Marey[12] called "le soulèvement de la valvule tricuspide" that which was later labeled the *c* wave. He noticed this wave in his intra-atrial curves. The genesis of the phlebographic *c* wave was correctly interpreted by François-Franck[14] and Fredericq.[11] Mackenzie,[7] however, felt that the *c* wave was due to the transmitted carotid pulsations, and this is still being mentioned.[6-11] Clinically this appears untenable, because the simultaneous recording of both carotid and jugular pulses shows that the *c*-wave peak precedes the carotid peak (Fig. 1) and because carotid impulse could scarcely explain the *c* wave in intra-atrial tracings. In 1906 Morrow[16] clamped the carotid, then slit it open to show that it did not bleed. The jugular tracings still showed the *c* wave. Bard[11] suggested that the aorta might be transmitting its pulsations through the atrium, while earlier Friedreich[11] and Potain[11] speculated that the same could happen through the large veins. Ewing[4] then disproved these possibilities by holding the aorta 2 cm. away from the mentioned structures with a retractor and muscarinizing the atrial muscle to avoid the creation of the second atrial wave, which coincides with the *c*

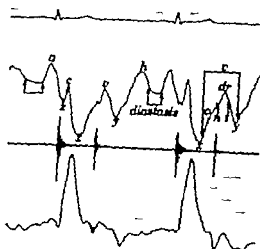


Fig. 1. ECG, phlebogram (PG) and phonocardiogram (PCG) of the pulmonic area, and the carotid pulse of normal 13-year-old boy. (Paper speed 50 mm. per second.)

*Wood originally used *z* to label the *h* or the level of diastasis.

Fundamentals of clinical cardiology

Dynamics of the normal jugular bulb pulsations and their changes in tricuspid regurgitation

A clinical revision with pertinent historical highlights

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There is no uniformity in the recording of venous pulsations. The rubber balloon,[1] the suction and the funnel-shaped cups,* the membrane cup,[2] the light beam,[3] and the contact-type transducer† point to the diversity of pickup devices. The site of recording varies from the external jugular vein, right or left, to the jugular bulb. The resulting dissimilarity of tracings, therefore, can be such as to defy comparisons and frustrate statistical analysis. Meanwhile, the intent in recording a phlebogram is to obtain a diagnostic and reference tracing reflecting the activity of the right atrium and ventricle. It has been pointed out, however, that some of these recording techniques may introduce instrumentation artifacts which distort the relationship between jugular pulsations and intracardiac events.[4] It would, therefore, appear that the standardization of recording techniques is a fundamental requirement if this mode of examination is to gain a solid foothold in clinical practice. Until this is accomplished one may justifiably question the value of the phlebogram as a clinical tool.

It is the purpose of this paper to show that the properly recorded phlebogram does, in fact, reflect quite faithfully the various phases of the activity of the right side of the heart, and to illustrate, on the example of tricuspid regurgitation, the usefulness of its application in heart disease.

Method and material

It has been shown experimentally that the accuracy of tracings increases in proportion to the closeness of the pickup device to the heart.[5] The right side of the neck and the jugular bulb, therefore, appear to be the logical choices. We use a funnel-shaped bell connected through a rubber tube to a piezoelectric crystal, which transforms pressure changes into electrical potentials.[6] The jugular bulb is usually approximated between the two insertions of the sternocleidomastoid muscle. Basically this is the technique used by Hartman,[5] Mackenzie,[7] and Tavel.[8] All abnor

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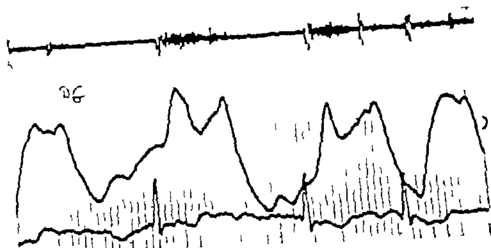


Fig. 3 PCG, PG, and ECG in case with atrial fibrillation. (Paper speed 75 mm. per second.)

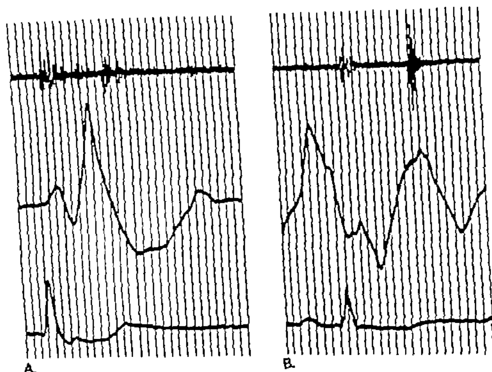


Fig. 4 PCG, PG and ECG in patient with A V nodal rhythm and retrograde conduction (*A*) and after restoration of normal sinus rhythm (*B*) (Paper speed 75 mm. per second.)

a distinct additional rise in the venous pulse. Ewing[4] named this the *diastolic rise d*. The effects of this motion were recognized before Ewing by François-Franck[14] and Fredericq,[15] but Ewing was the first one to show the two components of the *v* wave experimentally.[4] The transition from the *v* phase to the *dr* is usually marked by a small notch or a tiny incisura. This can be conveniently designated with the letter *n*. This is an important landmark because it indicates the beginning of ventricular isovolumic relaxation. It is at this point that the isovolumic relaxation induces the closure of semilunar valves. The *dr* continues until the ventricular pressure suddenly changes indicating the end of isovolumic relaxation and the beginning

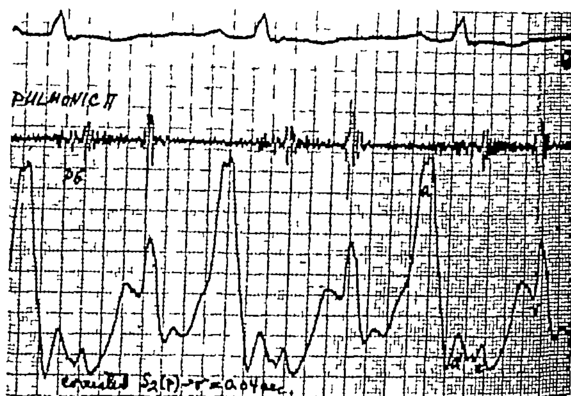


Fig 2 ECG PCG and PC in a case with prolonged P R interval (Paper speed 50 mm. per second)

deflection and could therefore mimic it The c wave was still there[4] The conclusion is that the c wave originates within the ventricle itself and that it reflects the isovolumic stiffening which causes the leaflets to balloon into the atrial cavity in the process of shutting them closed

The x The systolic depression or x results from two forces (1) atrial dilatation[11] responsible for some two thirds of it and (2) ventricular contraction effecting a pulling away motion of the A V ring from the atrium which is held back by the two cavae Ventricular contribution to the x was first postulated by François Franck[23] and Fredericq[14] although their premises were largely erroneous This ventricular activity accounts for up to one third of the dip Fig 1 shows the summation of these atrioventricular influences. If one now detracts the atrial contribution by observing the situation in atrial fibrillation (Fig 3) one can readily appreciate the marked reduction of the x depth Furthermore this illustration clearly shows that the varying depth of the x appears directly proportionate to the strength of the ventricular systole as expressed in a louder or less loud murmur The dominant atrial role in x genesis is further illustrated by nodal rhythm with retrograde conduction (Fig 4,A) Since both chambers now contract simultaneously the atrial portion of the x occurs later i e in early diastole. Restoration of normal sinus rhythm in this patient harmonizes once more the atrioventricular x creating activity (Fig 4 B)

The v The x trough represents the deepest fall in atrial pressure inducing an inflow of blood With this inflow the pressure will start rising This rise is called the v wave The v wave however is a composite phenomenon which consists of two phases. The forces creating the x trough represent the vis a fronte There is however a separate venous inflow component which will be more conveniently discussed with the dynamics of the h wave representing the vis a tergo These two combine in creating the *onflow phase o* of the v wave Morrow[15] coined the term first onflow wave Ewing[4] accepted the term onflow wave for the initial v wave segment. During this phase the atrium fills with inflowing blood At the peak of this filling however there ensues abruptly the ventricular isovolumic relaxation With it the A V boundary is suddenly thrust back toward the atrium This thrust produces an impact upon atrial contents manifested as

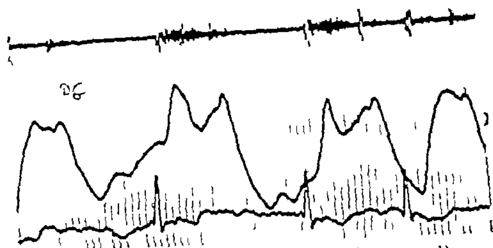


Fig. 3 PCG, PG, and ECG in a case with trial fibrillation. (P per speed 75 mm. per second.)

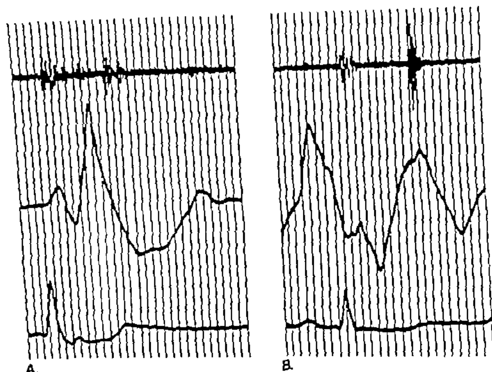


Fig. 4 PCG PG, nd ECG in patient with A-V nodal rhythm and retrograde conduction (*A*) nd after estoration of normal sinus rhythm (*B*) (Paper speed 75 mm. per second.)

a distinct additional rise in the venous pulse Ewing[4] named this the *diastolic* ise *dr* The effects of this motion were recognized before Ewing by François-Franck and Fredericq[11] but Ewing was the first one to show the two component of the *v* wave experimentall The *transition* from the *s* phase to the *dr* is usually marked by a small notch or a tiny incisura. This can be conveniently designated with the letter *n* This is an important landmark because t indicates the beginning of ventricular isovolumic relaxation It is at this point that the isovolum c relaxation induces the closure of semilunar valves. The *dr* continues until the ventricular pressure suddenly changes indicating the end of isovolumic relaxation and the beginning

of ventricular dilatation At this point the tricuspid valve opens and the tracing takes a final downward turn This transitional point we customarily mark with the letter *t*—for turn or transition Thus the duration of isovolumic relaxation can be measured by considering the *n t* interval

The v and h The downward deflection after the *t* point is due to ventricular dilatation [21] and the nadir of it carries the designation *y* In the beginning of this motion the A V valves open and there is then an uninterrupted veno-atrioventricular space Immediately preceding this motion the ventricle emptied itself and the atrium became filled With this motion the atrium dumps its contents into the ventricle This forward shift of blood however does not abolish the veno-cardiac gradient so that a slower phase of filling follows on the heels of this rapid initial forward propulsion The pressure rises to a rounded peak which is customarily designated with the symbol *h* We have mentioned that atrial dilatation creates a veno atrial gradient The ventricular dilatation likewise has a gradient creating effect The blood inflow however does not result from this vis a fronte only As Mackenzie[7] wrote If the blood in a superficial vein flowing towards the heart be intermittently stopped by pressure with the finger the vein visibly distends during the stoppage and collapses when the pressure is removed This distention clearly demonstrates a separate venous inflow component independent from direct influence of cardiac pulsations which results from a complex vis a tergo This cardiopetal flow is continuous although the closer to the heart the more it is modified by cardiac pulsations and intrathoracic pressures It is instrumental in the genesis of both the *o* phase (*v* wave) and the *h* deflection In a series of human studies Mackay and Walker[1] reaffirmed this and concluded that the *h* wave appears to be of venous origin and that it is simply reflected from the right side of the heart

The diastasis The summit of the *h* wave can be rounded peaked or it may simply represent a transition from a more rapidly rising curve into a horizontal or much slower rising segment. With the *h* peak the veno-atrioventricular space is now filled and only the ventricular compartment will be distended beyond this volume by atrial contraction in telediastole (Fig 1)

Amplitude relations and atrio-venous transmission In a normal phlebogram the *a* is usually the tallest wave and it should always be taller than the *v* peak with which it is compared The *c* is occasionally the highest point or it may be quite inconspicuous. The *h* wave can be higher or lower than the *v* wave but should not exceed the *a* wave crest The *x* trough is the deepest point while *z* and *y* should always be shallower

The *a* *c* and the *dr* (*v* wave) are best thought of as impact phenomena. One can then think of the *o* phase (*v* wave) and the *h* wave as atrial and atrioventricular filling phases respectively This distinction is important because the impact waves show a quick atrio-venous propagation with negligible time lag The filling phases, on the other hand are transmitted with delay because of lower pressures. This was measured experimentally[3]

It becomes necessary to stress that intra-atrial curves and external jugular tracings are not superimposable and that their differences can be even more pronounced in disease Three factors account for this (1) volume flow per unit time (2) the differences and changes in pressures, and (3) alterations in compliance Thus, the appreciable time lag between the atrial and jugular *o* phase (*v*) and the *h* wave becomes progressively shorter with rising pressures and/or reduced compliance. Likewise the relative amplitude and the angle of acclivity of the *o* phase and the *h* wave increase with the increased flow volume. These changes can become very conspicuous in the phlebogram at a time when intra-atrial tracings reflect still little or no change It is in this area that the phlebogram has a very special value

Tricuspid regurgitation

It is close to two and a half centuries since Lancisius[23] described the pulsations of the neck veins in tricuspid insufficiency It is over one hundred years since Bamberger[24] published the first graphic records of the venous pulse in tricuspid regurgitation and almost a quarter century since

Bloomfield and colleagues[illegible] published the intra-atrial curves of tricuspid incompetence. Yet a survey of the current status of tricuspid incompetence clearly shows that the diagnosis remains fraught with difficulty. Coelho,[illegible] for example, points out that one third of his patients with tricuspid regurgitation either gave only a slight suggestion of its presence or none at all. It seems trite to mention that the distended neck veins, peripheral edema, enlarged liver and so forth are neither specific nor essential for tricuspid regurgitation as they are for failure. Nor are the liver pulsations easy to appraise. Mackenzie[illegible] already was aware of the fact that cardiac pulsations, under certain circumstances, can be transmitted to the liver transdiaphragmatically—thus mimicking closely genuine liver pulsations. Therefore a liver which moves in unison with cardiac activity is not necessarily a pulsating liver. The systolic murmur need not be present. Thus, Scherf and Boyd[illegible] asserted that the tricuspid regurgitation is routinely present in a silent form, and that the finding of a murmur over the tricuspid area represents an exception to this rule. Zeh[illegible] likewise mentions a silent phase in some cases. Certainly autopsy reports with their high incidence of tricuspid valvular deformity would tend to lend credence to such statements.[illegible] Cases of tricuspid regurgitation without decompensation diagnosed clinically are rare but well known. On the other hand chronic failure without tricuspid regurgitation is much less of a rarity. Finally, failure and regurgitation can be combined. The recognition of all this is important, especially in cases requiring surgery. The most reliable way of making the diagnosis would be by angiographic studies with the use of preferably direct right ventricular puncture. To our knowledge this is not accepted practice. Thus, one is left with cardiac catheterization for presurgical diagnosis. Unfortunately this approach may be unreliable. In 1963 Braunwald and Awe[illegible] reported on normal left atrial pressure curves in the presence of severe mitral regurgitation. A year later Rubeiz, Nassar and Dagher[illegible] reported on normal contour of right atrial pressure curves in the presence of sinus rhythm and functional tricuspid regurgitation as diagnosed at surgery. From this they inferred that the recording of jugular pulse tracings was worthless, without, however, attempting to record any phlebograms.[illegible] That there is actual incongruity between atrial and phlebographic curves in certain cases of tricuspid regurgitation was pointed out by Hartman[3] in 1960. He was also the first one to appreciate the diagnostic significance of these incongruities, although he offered no explanation. Our experience is fully in agreement with these observations.

The three forms of tricuspid regurgitation. There are authors who make no diagnostic distinction between the two basic forms of insufficiency.[illegible] Others have attempted to separate the valvular from the annular variety by studying the tracings during ventricular systole, i.e., during the very act of regurgitation.[illegible] Although rarely mentioned, the early diastolic configurations have not been regarded as representing the characteristic differences between the two forms of incompetence.[illegible] As far as the phlebogram is concerned none of this appears in any way settled. It is our intention to show that there are indeed diagnosable differences.

Tricuspid regurgitation can be divided into the primary or valvular, secondary or annular, and mixed or valvulo-annular forms. The primary can be due to congenital conformity or it can be acquired. The etiology of acquired varieties may be inflammatory or neoplastic. The secondary insufficiency is always due to a dilated annulus, which, as a rule, develops with chronic elevation of pressures.[illegible] Clinically the isolated primary defect is rarely identified,[illegible] in contrast to the secondary insufficiency which is common. Common also is the associated congestive heart failure. As a matter of fact, secondary insufficiency is a facet of congestive failure. From this, three questions can be formulated: (1) What are the criteria necessary to distinguish uncomplicated congestive failure from failure with secondary insufficiency? (2) How do we diagnose the primary insufficiency (without failure)? and (3) Is it possible to identify primary incompetence obscured by secondary insufficiency with congestive failure?



Fig 5 These are tracings from a patient with mitral stenosis with retrograde transpulmonary rise in pressures. (Paper speed 75 mm. per second.)

Secondary (annular) regurgitation

Telediastole The underlying cause of secondary regurgitation is the systolic and diastolic pressure elevation This has to be chronic Transient unsustained elevations do not cause it [34] When the diastolic pressures are up the atrium will be emptying against these pressures The atrium will therefore hypertrophy and the *a* wave of the phlebogram will increase in amplitude (Fig 5) Chronologically that happens first i e even before regurgitation starts. Hypertrophy will thus effect proper atrial emptying in telediastole despite elevated pressures. The sustained elevation of diastolic pressure however will eventually result in overtaxing of the atrial muscle fiber Hypertrophy will be followed by dilatation and then the contractions weaken The *a* wave will then begin to show a progressively diminishing amplitude (Fig 6) Finally when the atrial muscle fiber becomes so stretched that it fails to accomplish any useful contraction atrial fibrillation supervenes and there is then no *a* wave in the phlebogram (Fig 7) When however atrial fibrillation develops earlier in mitral disease the described evolution of *a* wave may be interrupted at any stage

Systole the S and the J waves Meanwhile the elevation of systolic pressures leads to right ventricular hypertrophy and later on to ventricular dilatation. With it dilatation of the annulus occurs, and the blood then regurgitates from the ventricle into the atrium and eventually even into the large veins [32, 33] As long as the right atrium has enough compliance left this regurgitant blood is not likely to grossly affect the morphology of the right atrial pressure curve Thus in earlier stages of evolution cardiac catheterization is quite likely to meet with diagnostic failure. This was shown repeatedly on the operating table [3, 31] Phlebogram however is a better diagnostic tool in these early stages.

In normal conditions the venous pressure is just slightly above the right atrial pressure. With regurgitation into the right atrium and increase in systolic pressures in that chamber the vein will not be able to empty during systole with the ease that it used to The vein therefore will begin to distend In the phlebogram the early indication of this distention is seen when the *x* begins to shift to the left and becomes shallower The so-called *o* phase of the *v* wave no longer reflects a simple flow phe-

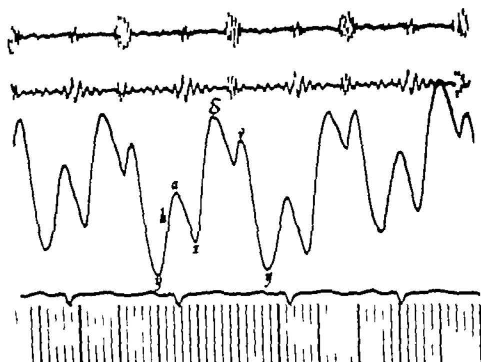


Fig. 6 PCG (two frequencies), PG, and ECG in a case of secondary tricuspid incompetence with still-preserved sinus rhythm. (Paper speed 75 mm. per second.)

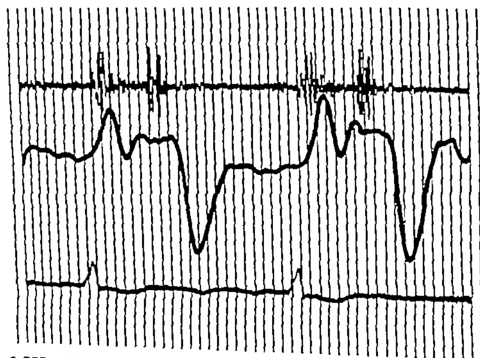


Fig. 7 PCG and PG in case of secondary tricuspid regurgitation with atrial fibrillation. (Paper speed 75 mm. per second.)

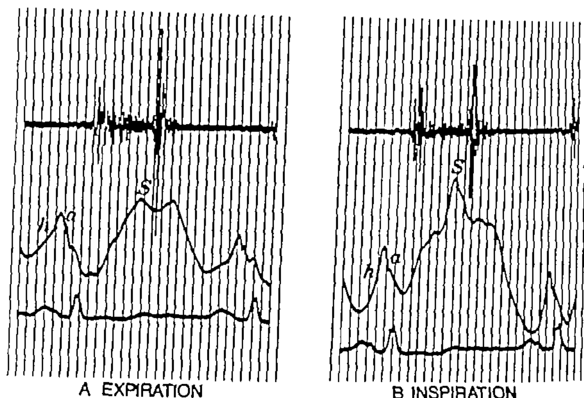


Fig 8 PCG PG and ECG in a case of mild to moderate secondary tricuspid regurgitation recorded at end of expiration (A) and end of inspiration (B) The patient was in congestive failure and was sitting in an upright position. (Paper speed 75 mm per second)

nomenon It evolves into a pressure flow curve which eventually forms a new wave[39] This is customarily labeled *S* This *S* wave makes its appearance in the phlebogram before the atrial pressure curve begins to mutate into the regurgitant form and figures are available to show at what pressure levels this takes place[33,34] With sufficiently high pressures and proportionate annular dilatation however the atrial *x* will be obliterated as well We can then say that it all begins when the phlebographic *S* wave commences to climb up the down slope of the *c* wave until it engulfs it partially or completely (Fig 6) In earlier stages meanwhile especially when the *c* is still identifiable one can perform a very simple maneuver to demonstrate the presence of regurgitation conclusively as was first shown in 1954 by Mueller and Shillingford[33] Our modification of their maneuver is as follows The patient has to be properly positioned This usually means elevating the patient until the continually distended veins begin to show respiratory oscillations In this position a phlebogram is recorded at the end of expiration If the *x* has shifted to the left i e the *x* has become shallower or obliterated one can ask the patient to breathe in and record the phlebogram at the end of inspiration If there is regurgitation the *S* wave will become so augmented that—if it has not done so already—it will climb up and often over the top of the *c* wave which may thus become completely drowned (Fig 8 *A* and *B*) Fig 9 shows simultaneous atrioventricular pressure curves in a patient with a well preserved *x* trough despite tricuspid regurgitation diagnosed by phlebography and confirmed at surgery The *S*-wave augmentation is usually seen with preserved sinus rhythm as shown in Fig 8 It can be observed however in tricuspid insufficiency with atrial fibrillation as well (Fig 10)

Finally when the disease reaches the stage of ventricularization the configuration of the right atrial pressure curves compared to the phlebographic tracings show close morphologic resemblance

With the development of atrial fibrillation the early systole becomes transformed by the appearance of a *J* wave first described by Weber[40] Later on Altmann[3] felt that the *J* wave was the pathognomonic feature of tricuspid incompetency Zeh[38]

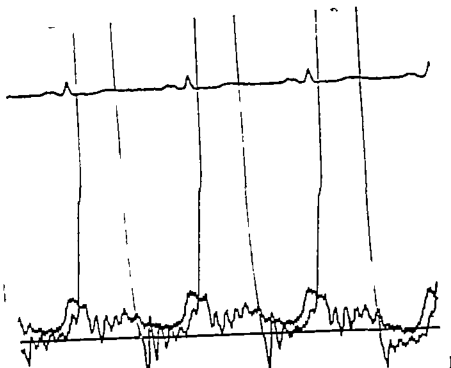


Fig. 9 ECG with simultaneous ventricular and atrial pressure curves in the same patient mentioned in Fig 8
(P per speed 75 mm. per second.)

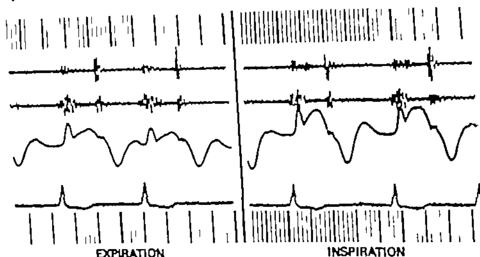


Fig. 10 PCG, PG, and ECG in case of secondary regurgitation with trial fibrillation, recorded i expira
and inspiration. (Paper speed 75 mm. per second.)

however denies it specifically Having re corded it quite frequently in simple atrial fibrillation we consider it to be a non-specific phenomenon It occurs, at least in its initial segment, during ventricular isovolumic contraction which coincides with

the *c* wave. Its peak, the highest in complex, suggests an exaggerated *c* wa This exaggeration is the probable con quence of an absent *a'* wave. Since floats" the leaflets into apposition lack of this approximation permits

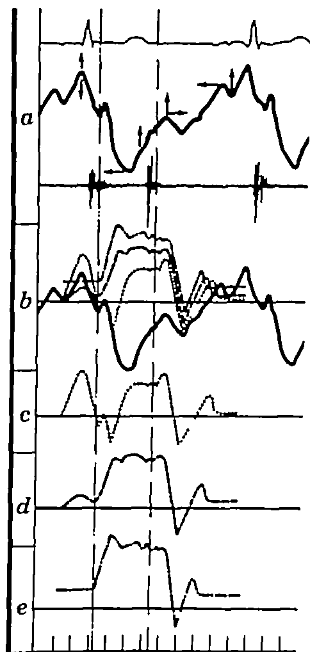


Fig 11 Development of secondary tricuspid in competence.
________ *a* normal tracing of a 12 year-old boy
c earlier changes
________ *d* midrange evolution with sinus rhythm
e, end stage (ventricularization) with atrial fibrillation. Arrows point to the direction of displacement of component fractions of the PG The characteristics are the *S* wave a precipitous *t y* drop and a steepening of *y-k* acclivity creating narrowing of the *t y-k* angle. The diastolic level rises progressively (Paper speed 50 mm. per second. Time line 0.1 second)

creation of a puff' at the time of ventricular isovolumic contraction Such puffs can be observed angiographically in atrial fibrillation The significance of the *J* wave consists in the fact that it is in part a transformed *c* and that the *S* wave fails to drown it (Figs. 7 and 10)

Proto and mesodiastole The changes, however are not confined to systole, i.e., to the very act of regurgitation As we said, the diastolic pressures are elevated as well. We have seen what happens to the *a* wave in telediastole In early diastole the atrium empties with the down-slope of the *v* wave. With occurrence of atrial fibrillation this is the only time the atrium can empty We should also recall that in systole the regurgitant blood causes a backward flow so that the greater forward flow now has to occur in diastole [23] Since the annulus is dilated and there is no obstruction the *y* will not be delayed and it will be deep Meanwhile because the pressures are elevated the *k* wave changes. The quality of this change is similar to the one that takes place during transformation of the *o* phase (*v* wave) into the *S* deflection The *k* wave, likewise ceases to be a simple flow phenomenon because the flow now has to take place under conditions of elevated pressures and reduced compliance The rise of the *k* wave in the phlebogram will therefore occur earlier The *k* wave thus becomes steeper and more prominent and we can witness a narrowing of the *v y-k* triangle (Fig 7) Since this change has to do with pressures and compliance it is, clearly not a feature peculiar to the tricuspid regurgitation per se It is nevertheless an indispensable portion of the total picture In judging the *k* wave however one must be cautious because as was shown on atrial curves [23] there is waxing and waning of the *h* with respiration and this can be greatly exaggerated in the phlebograms. All this is summarized graphically in Fig 11

Primary (valvular) incompetence

Systole and telediastole The phlebogram of primary incompetence differs from the secondary form This is so because the underlying dynamic factors are quite different To begin with we have no diastolic pressure elevations Thus the factor responsible for the increased strength of atrial contractions in telediastole is not there The systolic ventricular pressures are normal too in contradistinction to secondary incompetence What is not normal is that

these normal ventricular pressures are abnormally high for the atrium And this occurs at the *x* point, i.e., the time when atrial pressure should be at its lowest Quite obviously the *x* becomes increasingly shallower then obliterated and we are then observing the development of a regurgitant (*S*) wave (Fig 12) The atrial reaction to the systolic pressure elevation never does lead to a conspicuous phlebographic *a* wave —despite eventual atrial hypertrophy and enlargement. This, because of striking systolic *S* wave development being not only the first but also the most significant change. The prominence of this *S* wave then minimizes the comparative enlargement of the *a* wave. Finally atrial fibrillation can arrest this *a* wave evolution at any of its steps.

As stated the filling of the atrium from the ventricle even though the ventricle is of normal size, leads eventually to atrial overfilling hypertrophy and dilatation Meanwhile, the annulus remains undilated The dilated atrium stands in clear contrast to the normal size annulus and ventricle. This can be termed the atrio-annular disproportion and it has the effect of a relative stenosis. A filling diastolic murmur can therefore, be expected to develop.[41] As a consequence the *v*-wave descent will become delayed i.e. the *y* is going to occur late and the *k* will decrease in amplitude. This therefore, differs ostensibly from the secondary insufficiency with its deep undelayed *y* and a steep *k* (Fig 12)

Resolution of diagnostic perplexities. Confusion with actual stenosis occurs.[36,37] From the shape of the curves—both atrial and phlebographic—one cannot tell stenosis from insufficiency i.e. not when atrial fibrillation replaces sinus rhythm Fig 13 shows the superimposition of atrial and ventricular pressures obtained during a pullback The diastolic gradient is quite apparent At operation however there was no stenosis. Instead a shortened chorda kept the tricuspid open. The phlebogram of this case is shown in Fig 14 To reiterate, we are now analyzing the diastolic configuration of the phlebogram which is seen after atrial fibrillation develops. These are usually advanced changes and therefore more obvious. These diastolic events in

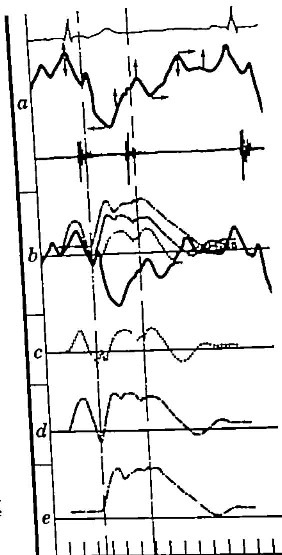


Fig. 12 Evolution of primary tricuspid incompetence.
———— normal tracing of 12 year-old boy
c, earlier changes
———— *d*, midrange changes
e, final configuration with atrial fibrillation. Arrows show the direction of shifting component parts of the PG. The salient features are the prominent *S* wave with slow *i-y* declivity and a smaller and obtunded *k*. (Paper speed 50 mm. per second. Time lines 0.1 second.)

tricuspid stenosis with sinus rhythm look quite different. As long as the atrium does not fail there is going to be a giant *a* wave Fig 13 shows the disproportion of the giant *a* wave to the diminutive *v* wave As one can readily see the "diminutiveness

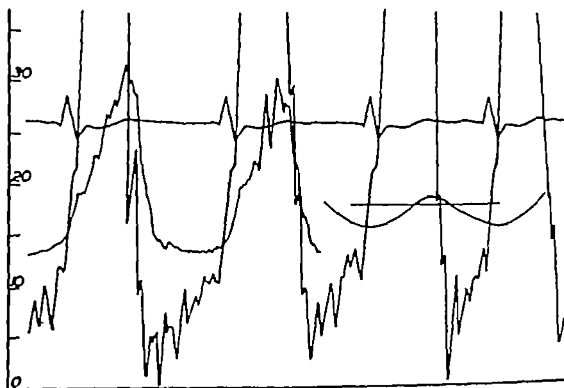


Fig. 13. Superimposition of atrial and ventricular pressure curves in a case of primary tricuspid regurgitation, complicated by retrograde pressure elevation secondary to mitral disease. There was no failure. (Paper speed 75 mm. per second.)

of the *v* wave is such that the gentleness of the *v y* declivity, i.e. the lateness of the *y* is by no means obvious. And if one looks at the configuration of an *a* wave produced by simple atrial hypertrophy as was seen earlier in pulmonary hypertension (Fig. 5) one can readily appreciate the difficulty of making the diagnosis of tricuspid stenosis in the presence of sinus rhythm and based on a single expiratory phlebogram. It is therefore essential that one has the presystolic murmur along the left sternal border and that there be no evidence of right ventricular hypertrophy. It is therefore much easier to appreciate tricuspid stenosis in atrial fibrillation. As pointed out before however when the atrium fibrillates the difference between actual stenosis and relative stenosis of primary tricuspid insufficiency becomes blurred. It is however still possible to distinguish them. To do so one has to exercise the patient as was first shown on atrial curves by McCord and associates.[22, 27] If there is actual stenosis the systolic portion of the tracing will not change but the diastolic one will. The *v y* descent namely becomes further delayed compared to the resting tracing. In fact the *y* may be so delayed that the *h* never does take place so that the *v* descent actually terminates with the rise of the obvious or obscured *c* or we may say the next systolic isovolumic upstroke. On the other hand when dealing with relative stenosis of tricuspid insufficiency the exercise will further accentuate the ventricularization of the systolic phase of the phlebogram while the *v* wave descent and therefore the *y* point will not change.

Mixed (valvulo-annular) forms. Plurivalvular involvement in rheumatic heart disease is common.[8, 23, 37, 41] Consequently tricuspid lesions are as a rule associated with the valvular involvement of the left side of the heart. In primary tricuspid insufficiency therefore the superimposition of the secondary regurgitation can be expected to occur at some later stage. What does this do to the morphology of the phlebogram? If we start with the contour of primary tricuspid regurgitation we notice that this does not change for a long time (Fig. 14). In this instance and despite retrograde elevations of pressures, the atrio-annular disproportion was still maintained there being no dilatation of the annulus and no secondary regurgitation. Why is this so? As we have already learned the atrium is

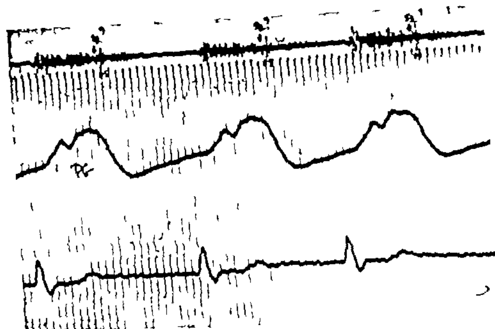


Fig. 14 PCG, PG and ECG in the same patient shown in Fig. 13 with tricuspid valve deformity (Paper speed 75 mm. per second.)

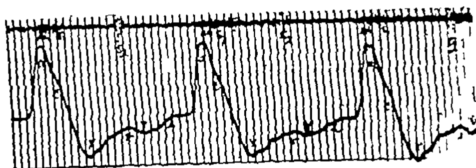


Fig. 15 PCG and PG in case of uncomplicated tricuspid obstruction due to a right trial myxoma with till-preserved sinus rhythm. (P per speed 75 mm. per second.)

both hypertrophied and dilated due to preceding systolic events (*S* wave) When retrograde elevation of pressures results in right ventricular hypertension the existing "leak" can become only more abundant. This means that the primary regurgitation has been made worse but at the same time this regurgitant blood decompresses some what the right ventricle. This decompression however is not enough to prevent the development of right ventricular hypertrophy During this stage of evolution the "atrio-annular disproportion will not be affected This will happen much later when the ventricle finally begins to dilate. Even then and because of pre-existing and marked atrial dilatation the ventricle cannot be expected to dilate sufficiently to catch-up with atrial dilatation until late in the process. It is for this reason that primary tricuspid insufficiency can be identifiable in the face of complicating secondary regurgitation This is exemplified in Fig 16,*A* The delayed *y* or slow *x* descent, resembles the primary form Additionally however there is an inspiratory *S*-wave augmentation, which proceeds to obliterate the *c* wave. The patient was in failure when the phlebograms in Fig 16,*A* were recorded The presence of failure then raises the question as to whether or not the inspiratory *S*-wave augmentation was related to

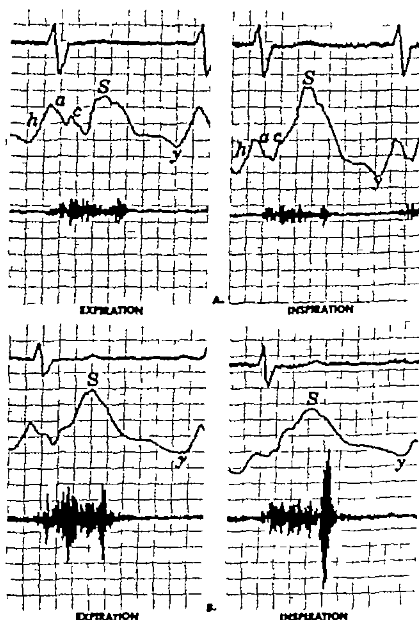


Fig. 16. ECG, PG, and PCG in a case of valvulo-annular (mixed) form of tricuspid regurgitation. A, recorded with patient in semiupright position because of congestive failure. B, obtained with patient in recumbent position after correction of f ilure. (Paper speed 50 mm. per second.)

failure and therefore to secondary tricuspid regurgitation. Furthermore, looking at the diastolic configuration, one has to ask whether the slow *v* descent with its delayed *y* was the function of underlying primary tricuspid regurgitation. It seems logical to assume that if the failure can be corrected and if this correction can eliminate the inspiratory *S* wave augmentation while the diastolic *v-y h* phase does not change, that we are then indeed dealing with a mixed form. The phlebograms in Fig. 16 *B* show this. The failure was corrected, the inspiratory *S*-wave augmentation was eliminated while the configuration of the diastolic portion indicative of primary incompetence remained unchanged.

We have discussed the phenomenon of *S* wave augmentation in secondary regurgitation. We have seen it as revealing a mixed form. The remaining question is whether it is characteristic of secondary regurgitation. This last example (Fig. 16,*A* and *B*) would definitely indicate so.

Conclusions

We would therefore like to suggest that the differentiation and demo i of th

two basic forms of tricuspid regurgitation can be accomplished with confidence by means of proper phlebographic technique. We further feel that the mixed forms should not be difficult to identify. With such information at hand the surgeon will be in a better position to decide whether to plicate, use a prosthetic replacement, or leave the tricuspid alone.

We wish to express our thanks to Dr. Irvin Ungar, Director of the Department of Applied Physiology at St. Mary Hospital, Long Beach, Calif., for his continuous encouragement and cooperation in furnishing much of the data utilized in this paper. Our special gratitude goes to Drs. Thomas L. Bohl and James S. Benedict who supplied the crucial information obtained at operation.

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Oxygen in ischemic heart disease

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Oxygen has been used for years in patients with ischemic heart disease without attention to its indication or effects both beneficial and detrimental. It has been assumed that an increase in arterial P_{O_2} would result in increased delivery of oxygen to hypoxic areas of the myocardium followed by improvement in cardiac function and hopefully prevention of fatal arrhythmias. Such clear-cut benefits have not been demonstrated as yet and, furthermore adverse effects of oxygen therapy on cardiac function have been reported as well as many toxic effects on other organs, the lungs in particular. This report will attempt to review some aspects of pulmonary oxygen toxicity, the physiology of oxygen transport, and its metabolic and hemodynamic effects on the ischemic heart.

Oxygen toxicity

The recent recognition of the toxic pulmonary effects of oxygen has resulted in increased respect for this gas which should now be considered a drug to be administered only when necessary and in proper dosage. Prolonged exposure to high concentrations of oxygen can result in pathologic changes in the lungs of both experimental animals and humans. These changes include intra alveolar hemorrhage, hyaline membrane formation, alveolar and interlobular septal edema, fibroblastic proliferation and hyperplasia of alveolar lining cells. The extent of pathology is related to the concentration of oxygen and time of exposure. There is debate as to whether the alveolar or the arterial P_{O_2} is the critical factor and there are conflicting experimental results as to its etiology. Some studies have shown that the creation of large venoarterial shunts, by causing arterial hypoxia, served to protect experimental animals from the effects of high inspired oxygen concentrations. This would suggest that intravascular oxygen tension is the determining factor and that patients with severe anoxia would, therefore, not be at risk. Others have found no such protective effect from the creation of such shunts, with similar degrees of pulmonary toxicity in cyanotic and acyanotic animals. Such data support the greater importance of alveolar P_{O_2}. Regardless of which is more crucial, it would appear that inhalation of oxygen in concentrations of less than 50 per cent is rarely toxic in humans.

Transportation of oxygen

Almost all the oxygen in the blood is carried in combination with hemoglobin with only a small portion dissolved in plasma. The amount of dissolved oxygen can be calculated by multiplying its solubility coefficient, 0.003, by the partial pressure

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of oxygen in the blood. This therefore accounts for only 1.5 per cent of the total oxygen content normally carried in arterial blood (0.3 c.c. per 100 c.c. of blood at a P_{O_2} of 100 mm. Hg). In spite of this dissolved oxygen is of the utmost importance since the tissues obtain oxygen from the dissolved fraction rather than from the red cell. Each gram of hemoglobin can carry 1.34 c.c. of oxygen when fully saturated. The degree of saturation is determined by the oxyhemoglobin dissociation curve. At a pH of 7.40 and a temperature of 38 degrees the P_{50} (partial pressure of oxygen at which hemoglobin is 50 per cent saturated) is 27.0 mm. Hg. A decrease in pH or a rise in temperature results in a shift of the curve to the right or, put another way, an elevation of the P_{50}. Since this represents a lessening of the affinity of oxygen for hemoglobin, oxygen is made more available for tissues under these conditions. Alkalosis or hypothermia have the opposite effect, and although the oxygen saturation and oxygen content go up with alkalosis, oxygen is more closely bound to hemoglobin and less accessible to tissues. These changes are acute and until recently were felt to be the only factors determining the binding of oxygen to hemoglobin. It has now been demonstrated that certain organic phosphates derived from the glycolytic cycle, 2,3-diphosphoglycerate (2,3-DPG) in particular, affect hemoglobin saturation in a major way.[8] An increase in the amount of 2,3-DPG in the red cell, because it binds with deoxyhemoglobin, results in a decreased affinity of hemoglobin for oxygen and an elevation of the P_{50}. Conversely, there will be stronger binding of oxygen to hemoglobin with a decrease in 2,3-DPG, since the common sites of binding that oxygen and 2,3-DPG share are now available. Under conditions of anoxia or anemia there is a rise in 2,3-DPG concentration which results in a shift of the oxyhemoglobin desaturation curve to the right and dissolved oxygen becomes more available. A fall in pH will result in increased 2,3-DPG levels. Thus, when acidosis first develops there is a shift of the curve to the right (Bohr effect) which occurs immediately. 2,3-DPG levels then decrease which results in a fall in P_{50} back toward its original level. The half time of this effect is about 6 hours. The opposite effect occurs after alkalosis causes a fall in P_{50} since 2,3-DPG concentration now increases and raises the P_{50}. In many clinical situations in which decreased amounts of oxygen are available, such as cyanotic heart disease, high altitude, cardiac failure, anemia, and lung disease, 2,3-DPG levels in the red cell increase, resulting in release of oxygen into solution with greater facility.

The availability of oxygen for myocardial metabolism is a complex situation. In order to evaluate the delivery of oxygen to ischemic areas or their bordering regions it would be most advantageous to be able to record the actual oxygen tension in the tissue being studied. Reliable techniques toward this purpose are not yet available. In lieu of this we rely on indirect parameters to assess the degree of hypoxia in the myocardium. Arterial and mixed venous P_{O_2} give us a general idea of the state of oxygenation of the whole body. The oxygen tension in coronary sinus blood (P_{CSO_2}) tells us something about the degree of cardiac hypoxia, if any. If the P_{CSO_2} is in the normal range we can assume adequacy of myocardial oxygenation. It must be remembered, however, that there may be small areas of the heart which are ischemic whose venous P_{O_2} may be extremely low but go unrecognized when mixed in with large amounts of blood with higher P_{O_2}.

Myocardial metabolism

Perhaps the most sensitive indicator of myocardial ischemia and anoxia is lactate balance. The myocardium is almost totally dependent on oxidative metabolism to maintain normal contractility.[9] Under normal circumstances enough oxygen is present to react with cytochrome A at the end of the electron transport chain. This allows for oxidative phosphorylation of ADP to ATP and for oxidation of flavin and nicotine coenzymes (FAD, NAD, NADP) which have been reduced in the citric acid cycle. After these coenzymes are again oxidized they are available for citric acid cycle reactions and utilization of acetyl CoA which is being produced from fatty acids and pyruvate. Under these conditions the myocardium actually extracts lactate and converts it to pyruvate and then to

acetyl CoA. During severe anoxia, electron transport is retarded and nicotine and flavin coenzymes accumulate in their reduced form. Citric acid utilization of acetyl CoA is slowed and glycolysis increases with the resultant accumulation of pyruvate. The decrease in NAD to NADH ratio results in reversal of the lactate-pyruvate reaction and production of lactic acid rather than extraction. An increase in lactate/pyruvate ratio in the coronary sinus blood (L/Pcs) or the demonstration of production of lactate would therefore, be taken as an indicator of myocardial hypoxia.

Anoxia following myocardial infarction

The evidence that oxygen is indicated in myocardial infarction is inconclusive. Great stress has recently been placed on the observation that arterial P_{O_2} is frequently lowered following an infarct. Various etiologies have been ascribed including pulmonary congestion, atelectasis, venous admixture and ventilation perfusion imbalances. Since P_{CO_2} is invariably normal it is not secondary to hypoventilation. In some cases rapid-acting diuretics have resulted in a rise in P_{O_2} suggesting heart failure as the etiology. There have been reports on a few patients with anoxia who do not become fully saturated with 100 per cent oxygen which would indicate the presence of shunts. Other investigators have found ventilation perfusion imbalance to be more commonly the cause of anoxia. There does seem to be a correlation between the severity of the patient's condition and the degree of anoxia with lower oxygen tensions in patients with shock and/or pulmonary edema. Valentine and associates[4] reported on a group of patients following acute myocardial infarction without pulmonary edema who had a mean P_{O_2} of 67.9 mm. Hg. Fillmore and co-workers[5] divided their patients into four clinical classes: those in the group without failure had a mean P_{O_2} of 86 mm. Hg while those with pulmonary edema had a mean of 60 mm. Hg. Most studies have found blood gas abnormalities in the majority of patients even when uncomplicated by heart failure. Since anatomic shunting plays only a small role in the production of hypoxemia,

the arterial P_{O_2} can be raised readily by increasing the inspired oxygen concentration.

Hemodynamic and metabolic effects of oxygen

The question to be answered is: Does correction of anoxia really help the patient or are there negative effects of oxygen administration which overshadow the potential benefits? Bourassa and colleagues[6] have demonstrated a decrease in cardiac index with an increase in mean systemic arterial pressure and peripheral vascular resistance after administration of 100 per cent oxygen to subjects with normal and abnormal coronary angiograms. Left ventricular work was decreased during oxygen breathing in the normal subjects and in patients with less than 50 per cent narrowing of the coronary vessels, however, it was unchanged in those with severe narrowing. In addition, in the latter group, especially those with significant three-vessel disease there was both decreased lactate extraction and even lactate production during oxygen breathing. Since the utilization of oxygen by the myocardium is relatively constant, a decrease in arterial P_{O_2} is accompanied by coronary vasodilatation and increased coronary blood flow in order to supply more oxygen. With an increase in arterial P_{O_2} the arterial–coronary sinus O_2 difference is increased, thereby requiring lower coronary flow. The authors suggest that during oxygen breathing in those patients with marked narrowing of their coronary arteries, coronary blood flow is decreased sufficiently to produce ischemic biochemical changes. Foster and associates[7] also found an increase in systemic resistance but no change in cardiac output in patients with myocardial infarction who breathed high concentrations of oxygen. They also noted a fall in blood lactate which suggested improved tissue oxygenation, but this finding may have been a function of time rather than be secondary to the increase in P_{O_2}. On the other hand, Kenmure and co-workers[8] found elevated arterial lactate levels in 22 of 37 patients with myocardial infarction which was especially marked in those with very low cardiac output and severe hypoxia. While breathing 90 per

of oxygen in the blood This therefore accounts for only 1 5 *per cent of the total* oxygen content normally carried *in arterial* blood (0 3 c c per 100 c c of blood at a P_{O_2} of 100 mm Hg) *In spite of this dis*solved oxygen is of the *utmost importance* since the tissues obtain oxygen from the dissolved fraction rather than from the red cell Each gram of hemoglobin can carry 1 34 c c of oxygen when fully saturated *The degree of saturation is determined by the oxyhemoglobin dissociation curve* At a pH of 7 40 *and a temperature of 38* degrees the P_{50} (partial pressure of oxygen at which hemoglobin is 50 per cent saturated) is 27 0 *mm Hg* A decrease in pH or a rise in temperature results in a shift of the curve to the right or put another way an elevation of the P_{50}. Since this represents a *lessening of the affinity of oxygen for hemo*globin oxygen is made more available for tissues under these conditions Alkalosis or *hypothermia* have the opposite effect and although the oxygen saturation and oxygen content go up with alkalosis oxygen is more closely bound to hemoglobin and less accessible to tissues These changes are acute and until recently were felt to be *the only factors determining the binding* of oxygen to hemoglobin It has now been demonstrated that certain organic phosphates derived from the glycolytic cycle 2 3-diphosphoglycerate (2 3 DPG) in particular affect hemoglobin saturation in a major way[3] An increase in the amount of 2 3 DPG in the red cell because it binds with deoxyhemoglobin results in a decreased affinity of hemoglobin for oxygen and an elevation of the P_{50} Conversely there will be stronger binding of oxygen to hemoglobin with a decrease in 2 3 DPG since the common sites of binding that *oxygen and 2 3 DPG share are now avail*able Under conditions of anoxia or anemia there is a rise in 2 3 DPG concentration which results in a shift of the oxyhemoglobin desaturation curve to the right and dissolved oxygen becomes more available A fall in pH will result in increased 2 3 DPG levels Thus when acidosis first develops there is a shift of the curve to the right (Bohr effect) which occurs immediately 2 3 DPG levels then decrease which results *in a fall* in P_{50} back toward its original level The half time of this effect is about 6 hours. The opposite effect occurs after *alkalosis* causes a *fall* in P_{50} since 2,3-DPG concentration now increases and raises the P_{50}. In many clinical situations in which *decreased amounts of* oxygen are available such as cyanotic heart disease high altitude cardiac failure anemia and lung disease 2 3 DPG levels in the red cell increase resulting in release of oxygen into solution with greater facility

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atmospheres of pressure) and increase in dissolved oxygen (about 5.0 volume per cent at 3 atmospheres) may have added advantage. Some animal studies do indicate a beneficial effect. Kline and associates[11] found that myocardial excess lactate, produced after induction of infarction either diminished or disappeared with administration of 100 per cent oxygen at 3 atmospheres, whereas 8 of 9 animals breathing room air at 1 atmosphere continued to produce excess lactate. This demonstrates a return to oxidative metabolism *in the hyperbaric treated animals*, while those breathing room air continue to rely on anaerobic metabolism. In addition hyperbaric oxygen appears to afford some protection against ventricular fibrillation following coronary artery occlusion in dogs and pigs. Smith and Lawson[12] occluded the circumflex branch of the left coronary artery in several groups of dogs. There was a 10 per cent mortality rate in those dogs breathing oxygen at 2 atmospheres compared to a 50 to 60 per cent mortality rate in those breathing room air or oxygen at 1 atmosphere.

While several animal studies indicate a more favorable prognosis with hyperbaric oxygen, there have not been any conclusive reports on patients, and the potentially toxic effects would seem to promote caution before advocating the use of hyperbaric oxygen.

Conclusion

The definitive evidence for the use of increased concentrations of inspired oxygen following myocardial infarction is not yet available. Neither is there convincing evidence that high P_O is actually detrimental to a favorable outcome in these patients. The weight of the studies to date seems to indicate that hypoxemia should be corrected and since hypoxia is so common with myocardial infarct, oxygen should be used in all cases. Since most of the studies showing adverse metabolic and hemodynamic effects used 100 per cent oxygen and toxic effects of oxygen are rarely seen with low inspired oxygen tensions, it would seem prudent to use supplemental oxygen at concentrations less than 50 per cent.

Oxygen masks are now available which utilize the Venturi principle to maintain constant inspired oxygen concentrations of 24, 28, 35 or 40 per cent. Since the anoxia secondary to myocardial infarction is virtually always immediately responsive to an increase in inspired P_O, such masks can be used without resorting to high oxygen tensions. In the present state of our knowledge it is probably unnecessary to generate an arterial P_O of more than 100 to 150 mm Hg. The combination of inspired oxygen concentrations between 24 and 40 per cent and normal levels of arterial P_O, should at best improve cardiac function by correcting tissue hypoxia around the infarcted area, prevent arrhythmias, and improve prognosis while at the least it will prevent oxygen toxicity.

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in 21 of these 22 patients which is biochemical evidence of a beneficial effect of oxygen This study also confirmed the fall in cardiac output with increase in arterial pressure and systemic resistance found by other workers There was also no change in left ventricular work during oxygen breathing

Changes in oxyhemoglobin dissociation: For and against the heart

It has been generally felt that ischemic changes in the myocardium are due to obstruction in the coronary vessels rather than hypoxemia per se and that extraction of oxygen increased in areas with low flow or that flow increased under conditions of anoxia thereby delivering more oxygen Cases of myocardial ischemia and necrosis have recently been described in young women with normal coronary angiograms.[9] Evidence of severe myocardial hypoxia in such cases has been demonstrated histologically by areas of subendocardial infarction and biochemically by myocardial lactate production and increased L/Pcs during periods of angina The reason for such changes in the absence of coronary artery disease is obscure Eliot and Bratt[9] propose an abnormal release of O_2 from hemoglobin Studies of myocardial oxygen tension have shown a decreasing gradient of P_{O_2} from the epicardium to the subendocardium Although the accuracy of such tissue oxygen tensions can be questioned the relative changes are probably real Since the tissue P_{O_2} of the subendocardium of the left ventricle is lower than the rest of the myocardium they feel this area is most sensitive to a decrease in available oxygen The fact that most of the pathologic changes following carbon monoxide poisoning occur in the subendocardium and papillary muscles supports this. In 14 of the 15 cases Eliot and Bratt studied there was abnormal hemoglobin-oxygen dissociation The abnormality however was an increase in P_{50} which should have resulted in greater availability of dissolved oxygen Perhaps as suggested by the authors the shift in P_{50} is really adaptive in nature rather than causative.

Whereas in the cases described previously abnormal oxyhemoglobin dissociation is presumed responsible for a diminished availability of oxygen the reverse effect can also occur An increased extraction of oxygen by ischemic myocardium has been demonstrated even in the absence of an elevated arterial P_{O_2} or a fall in coronary sinus P_{O_2} Under conditions of angina pectoris induced by rapid atrial pacing Shappell and colleagues[10] found a rise in the P_{50} of coronary sinus blood This was not accompanied by any changes in arterial P_O pH 2 3-DPG or lactate levels. In one patient the coronary sinus P_{50} was 2 9 mm Hg higher than arterial P_{50}. This resulted in an 8 per cent fall in hemoglobin saturation in coronary sinus blood Since the patient had an O_2 capacity of 21 7 volume per cent an additional 1 74 c.c. of oxygen per 100 c.c. of blood was delivered to the myocardium The mechanism of the shift in the oxyhemoglobin desaturation curve in these cases is as yet unknown This adaptive mechanism is limited by the extent of the change in P_{50}, whereas increasing the inspired O_2 concentration can insure high oxygen tension gradients between blood and myocardium and maximum O_2 content

The delivery of increased amounts of oxygen to ischemic areas of the myocardium should improve function Experimentally it has been shown that localized ischemia results in a decrease or cessation of contractility in the hypoxic area within seconds. In isolated rat hearts this can be reversed within 10 to 15 seconds by reinstitution of normal coronary flow and oxygenation[2] During periods of ischemia there is increased extraction of oxygen which is certainly facilitated by increasing the inspired O_2 concentration and thereby raising arterial P_{O_2} Since dissolved oxygen accounts for only a small portion of the O_2 content, one can add only a maximum of 2 c c of oxygen per 100 c c of blood even when breathing 100 per cent oxygen

Hyperbaric oxygen

Studies on the effect of hyperbaric oxygen have explored the possibility that the enormous P_O (about 1 600 mm Hg at 3

Inferior clockwise frontal plane forces in a child with endocardial cushion defect

The electrovectorcardiogram is said to be the sine qua non of the diagnosis of endocardial cushion defect or common atrioventricular canal. This abnormality is reported to be accompanied by superior counterclockwise forces in the frontal plane electrovectorcardiogram in virtually all cases. The finding of inferior clockwise forces in a patient with documented endocardial cushion defect initiated this report.

A six-year-old girl was admitted to University Hospital for cardiovascular diagnostic studies, having been referred for the evaluation of a heart murmur known to be present since birth. The child had moderate limitation of exercise tolerance. Physical examination revealed that the second heart sound was widely split throughout all phases of respiration, but was of normal intensity; there was a Grade III/VI harsh pansystolic murmur widely heard, but maximal at the low left sternal border; no diastolic murmurs were heard.

Radiologic examination revealed mild cardiomegaly with pulmonary vascularity slightly increased. Electrocardiogram (Fig. 1) showed first degree atrioventricular block and right bundle branch block with the mean electrical axis in the frontal plane at +60 degrees. Vectorcardiogram (Frank lead system) revealed QRS forces leftward, inferior and equal in the anterior-posterior direction. QRS depolarization in the frontal plane was clockwise in direction. A clinical diagnosis of ventricular septal defect with probable atrial septal defect was made. Cardiac catheterization revealed a moderately large increase in oxygen saturation at the right atrial level. Pressures were normal in all four cardiac chambers and in the pulmonary artery. There was no evidence of mitral or tricuspid regurgitation. The catheter entered the left atrium and left ventricle. Left ventricular biplane angiocardiography demonstrated a left-to-right ventricular shunt and deformity of the left ventricle typical of an endo-

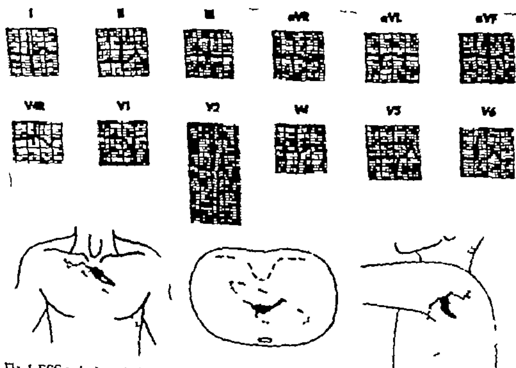


Fig. 1. ECG and schematic drawings of patient with endocardial cushion defect.

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nonexistent. Because of the lack of sufficient virologic laboratory support, viruses are not isolated, identified or adequately studied in patients.

The review of Loosli[1] attests to the frequency and importance of mixed viral and bacterial infections in disease. When Mogabgab[2] routinely sought for viruses as well as bacteria, he found high incidence of mixed viral and bacterial infections of the upper respiratory tract of man. A physician will never find viruses in patients if he never searches for them. Nor will he know if they are contributing to patient illness. Our own studies have shown that in experimental animals, at least, pericarditis, myocarditis, and mural and valvular endocarditis resembling lesions of rheumatic fever in man can be produced by viruses,[3-6] the lesions of which have never been produced with the Streptococcus or its toxins. But similar lesions were shown to be possibility for man as well.[6,7] The same is true for nephritis in both experimental animals and man.[8-10] On the other hand, the medical literature is replete with reports of patients with rheumatic fever or nephritis in whom bacteriologic investigations were made in which the Streptococcus was isolated and in whom the Streptococcus was considered the offending agent and even the sole one. But no simultaneous search was made for viruses to rule them out or in, as possible offenders. Why not? Maybe one or more viruses were the sole cause of the illness or necessary associated agents. The mere fact that bacteriologic study was made in which the physician or investigator found at least one bacterium considered pathogenic does not necessarily explain the pathogenesis of the patient illness. Until a thorough search is made for viruses as well as bacteria and until the agent isolated can be shown to be the only possible offender and to produce the illness experimentally the precise relative pathogenic role of bacteria and viruses remains unsolved.

Mixed infections of the respiratory tract, at least, exist and until such mixed infections are adequately considered, many clinical problems will remain obscure. This certainly applies to many cardiovascular and renal diseases. One can only find what one looks for; and until one looks and eliminates possibilities, the possibilities still remain. Bacteria and viruses as associated infections may be necessary for the production of certain disease states. One agent could serve as the necessary conditioning factor or adjuvant for the other. Clinical practice needs full access to virologic laboratories at least comparable to existing bacteriologic ones. Regional virologic laboratories are needed in the United States. Until these are available, a great deal concerning the pathogenesis and treatment of many disease states will remain obscure.

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Treatment of angina pectoris by nonmanual autostimulation of the carotid sinus

Carotid sinus massage has been reported to relieve the pain of angina pectoris, and relief by this means has been advocated as a test for angina pectoris. Recently investigators[1] reported on the electrical stimulation of the carotid sinus in the treatment of angina pectoris. We have had the opportunity to observe a patient who regularly obtains relief from angina pectoris by nonmanual autostimulation of his own carotid sinus.

The patient, a 52-year-old man, had angina pectoris for five years and, although his activities were severely limited, he still used between 3 to 10 nitro-

cardial cushion defect[4] including eccentric narrowing of the outflow tract forming a characteristic goose neck and a clearly visible mitral cleft.

Surgery was performed confirming that the patient had an endocardial cushion defect with a septum primum atrial defect and a cleft extending across the anterior leaflet of the mitral valve to the septal leaflet of the tricuspid valve as well as ventricular septal defects measuring 11 mm and 6 mm in diameter anterior to the ventricular defect associated with the cleft. Free floating segments of the atrioventricular valves formed their cephalad margins. Although the cleft was continuous across the mitral to the tricuspid valves there was sufficient tissue so that the edges abutted each other and there was no regurgitation at either valve. The septal leaflet of the tricuspid valve was small and moderately deformed. The anterior leaflet of the mitral valve was normal in appearance except for the cleft. Operative repair was accomplished. Postoperatively the child has had significant increase *in exercise tolerance and in growth and the chest* films are now normal.

This child had an endocardial cushion defect or *common atrioventricular canal without the electro*cardiographic-vectorcardiographic findings considered to be diagnostic of this lesion. Although incom*plete forms of this lesion occur without the charac*teristic electrocardiograms the only previous case reported of complete A V canal without superior counterclockwise frontal plane forces was complicated by an underdeveloped left ventricle.

The mechanism of the classical electrocardiographic and vectorcardiographic findings is said to be due to a congenital anomaly of the left bundle branch system.[5] This theory is supported by the persistence of the QRS abnormality following surgical correction. The reason for the absence of superior counterclockwise forces in this patient is unclear but is presumed to be due to sparing of her left bundle branch system.

The angiocardiographic diagnosis of endocardial cushion defect has been well described and is made *primarily from films of the left ventricle* in frontal projection. A deformity of the left ventricular outflow tract is produced by the anomalous attachment of the cleft anterior mitral leaflet to the inferior rim of the ventricular septal defect. The normally straight, smooth medial (septal) profile of the outflow tract is concave and irregular during systole. The superior and inferior components of the cleft anterior leaflet are separated by a thin radiolucent line representing the coapted edges of the superior and inferior leaflet segments. When the mitral valve *opens in diastole the deformity of the outflow tract* is maximal, showing a broad medial deformity where the anterior leaflet is attached in a low arc between *the aortic valve and the rim of the ventricular septal* defect. These angiocardiographic findings alerted the surgical team to the fact that the lesion was *more complicated than indicated* by the other clinical findings. It is suggested that left ventricular angiocardiography should be performed in patients with combined atrial and ventricular defects.

The patient described had an endocardial cushion defect documented angiocardiographically and at surgery. Electrovectorcardiographic findings were unusual in that the mean electrical axis in the frontal plane was inferior and associated with a clockwise inscription of the QRS loop. A review of the literature has failed to reveal additional cases of uncomplicated A V canal with inferior clockwise forces in the frontal plane.

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Mixed viral and bacterial infections

One usually finds what one looks for and one must *know what to search* For decades bacteriology has received considerable attention in clinical medicine. Bacterial diseases became well known and the rôle of bacteria in disease is fairly well understood Hospitals provide excellent bacteriologic laboratories to assist the physician in diagnosis and treatment of his patients. Then came the antibacterial drugs which revolutionized the practice of medicine and improved immeasurably the health of man. In the meantime viral infections have not received the attention they deserve in clinical medicine. Virologic *laboratories in hospitals or regions of the country* comparable to bacteriologic laboratories are virtually

nonexistent. Because of the lack of sufficient virologic laboratory support, viruses are not isolated, identified, or adequately studied in patients.

The review of Loosli[1] attests to the frequency and importance of mixed viral and bacterial infections in disease. When Mogabgab[2] routinely sought for viruses as well as bacteria, he found a high incidence of mixed viral and bacterial infections of the upper respiratory tract of man. A physician will never find viruses in patients if he never searches for them. Nor will he know if they are contributing to a patient's illness. Our own studies have shown that in experimental animals, at least, pericarditis, myocarditis, and mural and valvular endocarditis resembling lesions of rheumatic fever in man can be produced by viruses, the lesions of which have never been produced with the Streptococcus or its toxins. But similar lesions were shown to be possibility for man as well.[5-7] The same is true for nephritis in both experimental animals and man.[8-10] On the other hand, the medical literature is replete with reports of patients with rheumatic fever or nephritis in whom bacteriologic investigations were made in which the Streptococcus was isolated and in whom the Streptococcus was considered the offending agent and even the sole one. But no simultaneous search was made for viruses to rule them out or in, as possible offenders. Why not? Maybe one or more viruses were the sole cause of the illness or necessary associated agents. The mere fact that a bacteriologic study was made in which the physician or investigator found at least one bacterium considered pathogenic does not necessarily explain the pathogenesis of the patient's illness. Until thorough search is made for viruses as well as bacteria and until the agent isolated can be shown to be the only possible offender and to produce the illness experimentally the precise relative pathogenic role of bacteria and viruses remains unsolved.

Mixed infections of the respiratory tract, at least, exist, and until such mixed infections are adequately considered, many clinical problems will remain obscure. This certainly applies to many cardiovascular and renal diseases. One can only find what one looks for; and until one looks and eliminates possibilities, the possibilities still remain. Bacteria and viruses as associated infections may be necessary for the production of certain disease states. One agent could serve as the necessary conditioning factor or adjuvant for the other. Clinical practice needs full access to virologic laboratories at least comparable to existing bacteriologic ones. Regional virologic laboratories are needed in the United States. Until these are available, a great deal concerning the pathogenesis and treatment of many disease states will remain obscure.

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Carotid sinus massage has been reported to relieve the pain of angina pectoris, and relief by this means has been advocated as a test for angina pectoris. Recently investigators reported on the electrical stimulation of the carotid sinus in the treatment of angina pectoris. We have had the opportunity to observe a patient who regularly obtains relief from angina pectoris by nonmanual autostimulation of his own carotid sinus.

The patient, a 52-year-old man, had angina pectoris for five years and, although his activities were severely limited, he still used between 3 to 10 nitro-

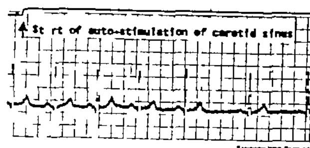


Fig 1 Slowing of heart rate with autostimulation of the carotid sinus. Lead II

glycerin tablets each day Selective cinecoronary arteriography demonstrated severe triple vascular coronary artery disease. Surgical treatment had been refused by the patient On a recent office visit the patient offhandedly inquired What do you think of these neck exercises for angina?" "What neck exercises I replied. The patient then demonstrated his neck exercises." While standing he held his breath in mid inspiration, extended his neck submaximally and appeared to tense his anterior neck muscles. He stated that this maneuver promptly caused cessation of chest pain whether the pain occurred at rest or after exercise and indicated that the same effect could be achieved by sharply turning his neck to the right. He warned that when turning the head to the right you have to be careful or you really go into a spin.' During the "neck exercises the pulse rate decreased sharply from 80 per minute to about 50 per minute. Slowing of the pulse was confirmed repeatedly electrocardiographically (Fig 1) Blood pressure, taken by the standard cuff method with the patient sitting was 150/80 mm. Hg before and 110/60 mm. Hg during the neck exercises. Further questioning of the patient revealed that some month ago he had read about vagal stimulation for relief of the pain of angina pectoris. He then practiced massaging his own carotid sinus and noted that he experienced complete relief of pain. On one occasion, while extending his neck in order to make the carotid sinus more accessible to himself he noted he had relief of pain by simple extension of the neck before manual massage was begun. Since that time he can at any time relieve his pain by either extending his neck or turning his neck to the right. Since he has used this technique, the patient has not had to use nitroglycerin except on rare occasions.

Relief of angina pectoris by carotid sinus stimulation is a consequence of lowered blood pressure, slower pulse, and decreased myocardial contractility with resultant lowered myocardial oxygen consumption.[1] Electrical stimulation of the carotid sinus nerve has been reported to be a useful method of treatment in some patients with intractable angina pectoris, but the technique is not without significant morbidity and mortality rates. The patient described above appears to be enjoying the benefits of carotid sinus nerve stimulation, but has avoided a surgical procedure of considerable magnitude. The intriguing possibility of training other patients to stimulate their own carotid sinus by this method is raised.

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The effect of exercise on some clinical measures of renal function

In our studies of renal function in relation to various intensities of physical activity we have emphasized certain clinical manifestations of exercise which may have important diagnostic and possibly therapeutic implications. Our purpose here is to summarize the results of our previous investigations. -4

In a definitive study of the effect of exercise on renal function, a spectrum of stimuli must be considered. Previous tudies claim that heavy exercise reduces glomerular filtration, reduces urine volume with a concomitant increase in urine osmolal concentration, increases urinary acidity and elicits proteinuria, microscopic hematuria and cylindruria, i.e. produces the athletic pseudonephritis of Gardner The effects of mild and moderate exercise on these renal variables appear never to have been studied in a systematic manner

Five healthy men none with a history of renal disease, served as subjects. Each subject either walked at 5 6 km. per hour or jogged at 8.0 km. per hour or ran at 10.5 km. per hour for one hour on a horizontal motor-driven treadmill in a constant environment maintained at 16° C. dry-bulb and 11 C. wet-bulb Each experiment was preceded by a one hour rest period. The effect of a given exercise task on a renal function variable was evaluated by comparing an exercise value to a corresponding rest value.

Some results of these experiments are presented in Figs. 1 to 3 Endogenous creatinine clearance, assumed to correlate with glomerular filtration, decreased during heavy exercise. During moderate exercise it did not change, and during mild exercise it increased (Fig 1) An antidiuresis occurred in all

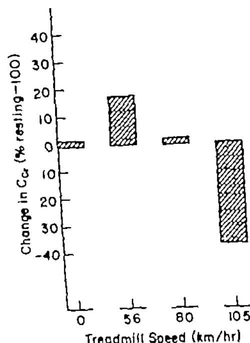


Fig. 1 Changes in creatinine clearance during exercise.

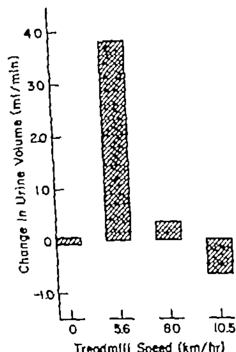


Fig. 2 Changes in urine excretion during exercise.

subjects during heavy exercise (Fig. 2). During mild exercise, however, there was diuretic effect and during moderate exercise an antidiuresis per se did not occur. The renal concentrating ability of the kidney appeared to be interrupted during heavy exercise. Fig. 3 indicates that the exercise urine for every rate of exercise was less concentrated than for rest. During mild and moderate exercise, these results appear to be in accord with the urine-volume data which demonstrated no antidiuretic effect. During heavy exercise, however an opposite trend appeared to be initiated whereby more dilute urine than for rest or moderate exercise was excreted, despite the antidiuresis which did occur. With respect to urinary acidity shift toward more acidic urine occurred during the two higher rates of exercise. The urine passed after mild exercise, however as more alkaline than for rest. Microscopic examination of the exercise and rest urine specimens showed that rates of excretion for red cells and both hyaline and granular casts increased with increasing rates of exercise. The excretion rates for epithelial cells and white cells did not appear systematically related to exercise rate. In the case of heavy exercise proteinuria as noted more frequently than in the cases of mild and moderate exercise.

In our experience, cylindruria after exercise is found only in the presence of acidic urine, proteinuria, and low rate of urine flow. According to McQueen, who used normal and nephrotic patients and in vitro system, hyaline casts are precipitates of Tamm-Horsfall mucoprotein, plasma proteins acting as precipitating agents. The effect of NaCl on this physical chemical interaction was found to be inhibitory. Therefore we feel that cylindruria in relation to the athletic pseudonephritis of Gardner will occur only when the necessary conditions are met: namely sufficient concentrations of Tamm-Horsfall mucoprotein and plasma proteins, a low concentration of NaCl, an acid medium, and low rate of urine flow. The latter condition is in accord with the data of Patel who studied healthy men after exercise and appears necessary in the case of normal subjects since the concentrations of Tamm-Horsfall mucoprotein and plasma proteins would tend to increase and a greater period of time would be allowed for their interaction in the distal portion of the nephron where casts are presumably formed.

With respect to the observation of an increasing tendency for proteinuria, microscopic hematuria, and cylindruria with heavy exercise, the question was raised concerning the regularity of these phenomena with very severe exercise. Pre- and postrace urine specimens were obtained from 77 well-trained cross-country runners who competed in and finished a 20 km. race. The rate of protein excretion increased above prerace value in 41 of 51 men studied for proteinuria. The nature of organized sediment was studied in the pre- and postrace urine specimens of 52 men, some of whom were randomly considered for proteinuria. Microscopic hematuria was observed in 31 per cent of the postrace urine specimens, and in 10 per cent of the prerace urine specimens. Hyaline casts were observed in 42 per cent of the postrace specimens, and 6 per cent of the prerace specimens. Granular casts were observed in 77 per cent of the postrace specimens, and in 6 per cent of the prerace specimens. White cells and epithelial cells were also associated with exercise—92 per cent of the postrace and 52 per cent of the prerace urine

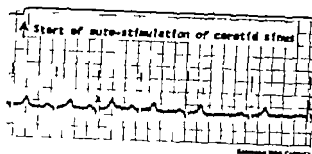


Fig. 1. Slowing of heart rate with autostimulation of the carotid sinus. Lead II.

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The effect of exercise on some clinical measures of renal function

In our studies of renal function in relation to various intensities of physical activity, we have emphasized certain clinical manifestations of exercise which may have important diagnostic and possibly therapeutic implications. Our purpose here is to summarize the results of our previous investigations.[1-3]

In a definitive study of the effect of exercise on renal function, a spectrum of stimuli must be considered. Previous studies claim that heavy exercise reduces glomerular filtration, reduces urine volume, with a concomitant increase in urine osmolal concentration, increases urinary acidity, and elicits proteinuria, microscopic hematuria, and cylindruria, i.e., produces the athletic pseudonephritis of Gardner.[4] The effects of mild and moderate exercise on these renal variables appear never to have been studied in a systematic manner.

Five healthy men, none with a history of renal disease, served as subjects. Each subject either walked at 5.6 km. per hour or jogged at 8.0 km. per hour or ran at 10.5 km. per hour for one hour on a horizontal motor-driven treadmill in a constant environment maintained at 16° C. dry-bulb and 11° C. wet bulb. Each experiment was preceded by a one-hour rest period. The effect of a given exercise task on a renal function variable was evaluated by comparing an exercise value to a corresponding rest value.

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Letters to the Editor

Variations in the diastolic threshold

To the Editor:

Dr Rogel and his associates, in the September 1970, issue of the AMERICAN HEART JOURNAL, describe an increase in the excitability of the dog heart following extrasystoles and attribute it to changes in ventricular excitability induced by the extra beat. They state that the shortening of the cycle length induced by the extrasystoles cannot entirely explain this phenomenon. I would like to take exception to this statement. In Fig 3 A the extrasystole preceded the following S_1 by 40 msec., and consequently the first effective S_1 occurred 40 msec. later in the ventricular cycle (at a time of higher excitability compared to the preceding ineffective S_1 stimuli). The second effective S_1 was preceded by three cycles shorter than the basic driving cycle length. As a result of this the heart rate increased, and therefore the Q-T intervals following the extrasystole were shorter than those preceding the extrasystole. Since S_1-S_1 was kept constant, all S_1 following the extrasystole fell later in the ventricular cycle. A similar phenomenon is also seen in Figs. 3 B and C, 4 A and 5. Thus, rate-induced shortening of the ventricular repolarization time and of refractory period duration caused the S_1 stimuli to fall later in the cycle at a time of increasing excitability and to become, therefore, effective.[2-4]

In human and dog hearts, we found diastolic threshold variations similar to the variations described by Rogel and associates, during the relative refractory period. We have designated[5,6] the stimulus intensity interval confining these variations as the "threshold interval." The values T and T in the paper by Rogel and associates correspond to the limits of the threshold interval as defined by us. In our studies, the probability for excitatory responses to the testing stimuli was directly proportional to the stimulus intensity within the limits of the threshold interval. The curve depicting this relationship has a sigmoid shape.

Years ago, Blair and Erlanger[7,8] described similar spontaneous variations of the excitability of the sciatic-phalangeal nerve preparation of Rana pipiens. They also noticed a direct relationship between the probability for excitatory responses and the intensity of the testing stimuli in this preparation just as we did in the heart of the dog and man. Pecher[9] confirmed their observations and also found a sigmoid relationship between the probability for excitation and the intensity of the testing stimuli in the nerve which we later noted in the heart.

The mechanism underlying these variations is not clear. I have recently observed (unpublished data) variations in the diastolic threshold of calf Purkinje fibers by using the conventional microelectrode technique for intracellular recording and stimulation. In one case, for example, the threshold variations were confined to a threshold interval of 2×10^{-7}-1×10^{-6} Amperes. The diastolic membrane potential was steady during the time of observation. It would appear from this that the threshold variations cannot be related to oscillations of the membrane potential.

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Reply

To the Editor:

We wish to thank Dr. Arbel for his interesting remarks. It is true that there seems to be some resemblance between the threshold interval described by him and the T_H-T_L phenomenon of our studies. However, Dr. Arbel's observations are related to threshold changes only in the diastole and only to a given interval, while our experiments describe dynamically a wide range of variations throughout the entire cardiac cycle. Dr. Arbel draws his conclusions from the calculated probability that a certain current level has in order to provoke

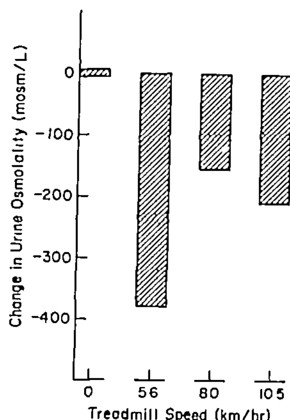


Fig 3 Changes in urine osmolality during exercise.

specimens contained white cells, and 54 per cent of the postrace and 35 per cent of the prerace specimens contained epithelial cells.

These results demonstrate that in healthy men under normal conditions the effect of exercise on some measures of renal function is differential. Mild exercise may increase a function, wh le severe exercise may decrease it. In the cases of proteinuria, microscopic hematuria, and cylindruria in healthy men, the degree of each appears to be proportional to the relative severity of exercise. The diagnostic implication of these data is that the concurrent state of activity of a patient should be controlled or at least known for adequate interpretation in the differential diagnosis of renal disease. Therapeutically our data suggest that medically supervised studies of mild exercise should be conducted on patients with renal disease to determine if the diseased state can be improved.

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Erratum

The article by Phillips, Macken, and Rugh entitled "Pathologic sequelae of acute cardiac irradiation in monkeys, which appeared on pp. 528 to 542 of the April, 1971 issue of the JOURNAL, carried several incorrect figure legends.

The following changes should be made The legend under Fig 4 on p. 531 should be placed under Fig 7 on p. 533 the legend under Fig 7 on p. 533 should be placed under Fig 8 on p. 534 the legend under Fig 8 on p. 534 should be placed under Fig 9 on p. 534 the legend under Fig 9 on p. 534 should be placed under Fig 10 on p. 535 the legend under Fig 10 on p. 535 should be placed under Fig 4 on p. 531

Reprints of this article in its correct form are available upon request. Address Dr Roberts Rugh, Department of Radiology 630 West 168th Street, New York, N Y 10032.

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Variations in the diastolic threshold

To the Editor:

Dr Rogel and his associates, in the September 1970, issue of the AMERICAN HEART JOURNAL, describe an increase in the excitability of the dog heart *following* extrasystoles and attribute it to changes in ventricular excitability induced by the extra beat. They state that the shortening of the cycle length induced by the extrasystoles cannot entirely explain this phenomenon. I would like to take exception to this statement. In Fig. 3 *A* the extrasystole preceded the following S by 40 msec and consequently the first effective S_1 occurred 40 msec. later in the ventricular cycle (at time of higher excitability compared to the preceding ineffective S_0 stimuli). The second effective S_1 was preceded by three cycles shorter than the basic driving cycle length. As result of this the heart rate increased, and therefore the Q-T intervals following the extrasystole were shorter than those preceding the extrasystole. Since S_T-S_1 was kept constant, all S_1 (following the extrasystole) fell later in the ventricular cycle. A similar phenomenon is also seen in Figs. 3 *B* and *C*, 4 *A* and 5. Thus, rate-induced shortening of the ventricular repolarization time and of refractory period duration caused the S_1 stimuli to fall later in the cycle at time of increasing excitability and to become, therefore effective.[2-4]

In human and dog hearts, we found diastolic threshold variations similar to the variations described by Rogel and associates, during the relative refractory period. We have designated[5,6] the stimulus intensity interval confining these variations as the "threshold interval." The values T_H and T in the paper by Rogel and associates correspond to the limits of the threshold interval as defined by us. In our studies, the probability for excitatory responses to the testing stimuli was directly proportional to the stimulus intensity within the limits of the threshold interval. The curve depicting this relationship has sigmoid shape.

Years ago, Blair and Erlanger described similar spontaneous variations of the excitability of the sciatic-phalangeal nerve preparation of *Rana pipiens*. They also noticed direct relationship between the probability for excitatory responses and the intensity of the testing stimuli in this preparation just as we did in the heart of the dog and man. Pecher[9] confirmed their observations and also found sigmoid relationship between the probability for excitation and the intensity of the testing stimuli in the nerve which we later noted in the heart.

The mechanism underlying these variations is not clear. I have recently observed (unpublished data) variations in the diastolic threshold of calf *Purkinje* fibers by using the conventional microelectrode technique for intracellular recording and stimulation. In one case for example the threshold variations were confined to threshold interval of 2×10^{-7}-4×10^{-7} Amperes. The diastolic membrane potential was steady during the time of observation. It would appear from this that the threshold variations cannot be related to oscillations of the membrane potential.

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Reply

To the Editor:

We wish to thank Dr. Arbel for his interesting remarks. It is true that there seems to be some resemblance between the threshold interval described by him and the T_H-T_L phenomenon of our studies. However, Dr. Arbel's observations are related to threshold changes only in the diastole and only to given interval, while our experiments describe dynamically the range of variations throughout the entire cardiac cycle. Dr. Arbel draws his conclusions from the calculated probability that certain current level has in order to provoke

depolarization at a single diastolic interval The direct relationship between the current level and the changes of depolarization seems to be very unlikely since every successful stimulation enhances and influences further the probability of the next success. It may be, therefore advisable to include these thoughts into his calculations—provided we under stand correctly Dr Arbel s abstracts.

In our article doubts have been raised as to the importance of the changing width of action potential as the only causative mechanism in the threshold reducing effect of an extrasystole Dr Arbel takes exception to this statement. However shortening of the action potential would hardly explain why the T_D and T_L curves are so different in shape. It would also be inadequate to explain why a subthreshold S_n applied in the diastole becomes effective. A shortened cycle length would influence only S_f given in the relative refractory period but would not have any effect later in diastole Since extrasystoles do induce changes in T_D and T_L levels also during the diastolic period, a mechanism other than shortened cycle length must be considered Furthermore it would also be unlikely that a single extrasystole would lower the threshold for a number of consecutive cycles if the mechanism was only a shortening of a single action potential. A subthreshold stimulus may remain ineffective immediately following an extrasystole but becomes a de polarizing one in the successive beats. Dr Arbel s assumptions are not applicable to such phenomena The development of a snowball phenomenon, shown in our study is an additional example which is inadequately explained by a shortened cycle length The oscillation of membrane potential suggested in one of Dr Arbel s abstracts, seems now to be denied according to his own microelectrode studies We are awaiting the full description of his various experiments which are of interest but unpublished as yet.

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Salivary gland hemorrhage as a complication of anticoagulation therapy

To the Editor

We recently published an article entitled Salivary gland hemorrhage—An unusual complication of Coumadin anticoagulation by DeCastro, Hall, and Glasser (AMER. HEART J 80:675 1970) I recently had the occasion to see an almost identical case, which was surprising since this has been such an unusual complication.

The patient was a 50-year-old man who had placement of a Starr Edwards mitral valve prosthesis for mitral insufficiency done in 1964 He had been on continuous anticoagulation therapy since. Although he had been somewhat difficult to control in therapeutic range, he had had no major hemorrhagic complications. One day prior to admission he noted the onset of bleeding gums and a blood clot under his tongue (Fig 1) His physical examination was otherwise unchanged except for extension of the hematoma to the right submandibular area (Fig 2) His prothrombin time was 53 seconds with a control of 13 seconds. There was rapid resolution following temporary discontinuation of the Coumadin.

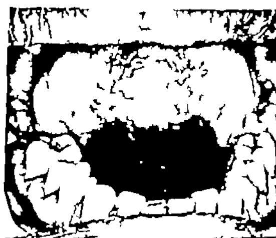


Fig 1



Fig 2

It is of interest that in each instance this complication occurred in a patient with a prosthetic heart valve. This certainly doesn t document a relationship between the two, however with the additional destruction of red cells and platelets secondary to these valves, such a relationship might exist.

In any case we thought this add tional case might be of i terest.

Stephen P Glasser Major (MC) USA
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Table I. The monthly distribution of the postcardiotomy syndrome in the years 1966 to 1970

	Jan	Feb	March	April	May	June	July	Aug	Sept	Oct.	Nov	Dec
1966												
Cardiac operations	8	8	14	7	3	7	0	7	11	12	10	7
Postcardiotomy syndromes	0	0	0	0	0	1	0	1	0	0	0	0
1967												
Cardiac operations	13	11	12	16	16	18	0	7	14	22	21	9
Postcardiotomy syndromes	1	0	1	1	1	1	0	0	2	1	1	1
1968												
Cardiac operations	17	11	6	19	17	12	0	8	24	27	23	13
Postcardiotomy syndromes	1	0	1	1	2	4	0	0	0	1	0	0
1969												
Cardiac operations	14	17	16	11	18	12	0	5	28	28	19	15
Postcardiotomy syndromes	0	1	1	2	1	1	0	1	0	1	1	1
1970												
Cardiac operations	10	23	16	15	12	10						
Postcardiotomy syndromes	0	2	3	1	0	1						

Postcardiotomy syndrome—An infectious disease?

To the Editor:

An interesting annotation was recently published in this JOURNAL (AMER. HEART J. 80:290, 1970) in which the possibility of an infectious (viral) origin of postcardiotomy and postinfarction syndromes was emphasized.

Since we had a clinical impression that individuals with these syndromes tend to present themselves in clusters, the possibility of an infectious cause has often been discussed in our clinic. If epidemic occurrence could be demonstrated, this would be in favor of the infection theory. We, therefore, went through all records on patients submitted to cardiac operations since the beginning of the year 1966, when our new hospital was opened, until the end of June, 1970, in an attempt to discover all the cases of postcardiotomy syndrome.

The total number of patients who had undergone heart operations during these 4½ years was 822, and in 690 cases enough information was found to enable us to diagnose with reasonable certainty the presence or absence of a postcardiotomy syndrome. The operations included (in order of frequency) mitral commissurotomy, occlusion of an atrial septal defect, resection of an aortic coarctation, ligation of a patent ductus arteriosus, insertion of an aortic valve prosthesis, and others. The patients usually stayed in the hospital for 3 to 4 weeks after the operation and were seen at the outpatient department for 2 to 3 months thereafter.

The number of postcardiotomy syndromes was 39 (5.7 per cent). Only patients with distinct signs of pericarditis with a good response to steroid therapy were included. The distribution of the cases of postcardiotomy syndrome from January, 1966, to June, 1970, is shown in Table I. The distribution turned out to be unexpectedly even, with few small clusters. The number of cases per month is too small to allow proper statistical treatment. If considered in half-year periods the frequency of its occurrence does not differ significantly (χ^2 11.4(8) 0.1 $< p <$ 0.2) from an expected distribution based on the over-all frequency of the syndrome and the number of cardiac operations performed during each half year period. Thus, our material did not demonstrate epidemic tendency in the occurrence of the postcardiotomy syndrome. This naturally does not exclude an infectious etiology. Further studies along the lines drawn in the annotation referred to above will probably solve the problem in the future.

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We recently published an article entitled 'Salivary gland hemorrhage—An unusual *complication* of Coumadin anticoagulation" by DeCastro Hall and Glasser (AMER. HEART J 80:675 1970) I recently had the occasion to see an almost identical case, which was surprising since this has been such an unusual complication.

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encountered in warm areas of the world, which earlier writers failed to realize. Gottlach has produced a book which really consists of a series of short papers. From the undergraduate student standpoint this book lacks chapters concerning the normal kidney classifications and diagnosis of renal disease, method for study and definition of renal function, basic principles of normal and abnormal renal physiology and pathology details of urinalysis, and basic principles in therapeutics. Those who are well informed in such matters will find this to be a useful book.

THE COMPUTER A MEDICAL TOOL (COMPUTER WERKZEUG DER MEDIZIN). Edited by C. Th. Ehlers, N. Hollberg, and A. Proppe, Berlin, Heidelberg, and New York, 1970, Springer-Verlag, 258 pages.

This volume represents the Proceedings of a Colloquium on Data Processing in Medicine which was held October 7 to 9 1968 in Erbach im Rheingau, Germany. It was intended to provide clinicians with no prior exposure to medical computer applications some insight into the great variety of problems which may be encountered with this new tool. The papers range from didactic presentations on the basic structure and functions of computers to the description of dream models of medical diagnosis (Proppe). Although the American reader is constantly reminded of similar meetings in the United States in the early fifties, it is noteworthy that their European counterparts try diligently to avoid the lure of some of the utopian abstractions which were common in these early days. As compared to other Western European countries, Germany became involved in medical data processing relatively late. Those who are involved in this work at present appear to be well informed about progress elsewhere but their preoccupation remains limited to the study of this progress, and few new or original concepts are being contributed at this time. The papers dealing with cardiological problems such as electrocardiography or CCU monitoring are rather noninformative particularly for the American reader. As an introduction into the subject of medical electronic data processing, this volume is not sufficiently systematic.

Book reviews

PLATELETS AND THE VESSEL WALL FIBRIN DEPOSITION Symposium of the European Atherosclerosis Group June 15 17 1969 Edited by Gotthard Schettler Stuttgart 1970, Georg Thieme Verlag 188 pages.

The recent surge of interest in the role of platelets in thrombus formation makes timely these proceedings of a symposium on atherosclerosis held in Germany during June of 1969 The role of platelets and wall-fibrin depositions in the production of atherosclerosis does need clarification. There are those who consider these deposits the cause of atherosclerosis whereas others remain dubious. A large number of investigators from the European nations gathered to discuss many facets of this problem. The main topics included aspects of morphology and biochemistry of blood platelets, effects of various agents on platelet formation and platelet fibrin vessel wall interactions. Most of the papers are related to experimental studies in the laboratory only a few being clinically oriented This is as it should be at this time. The presentations are brief clear succinct and well presented This is an excellent review of some of the studies in progress in European centers on this important subject.

AUSCULTATION OF THE HEART AND PHONOCARDIOGRAPHY By Aubrey Leatham, M B F R C P London 1970, J & A. Churchill, Ltd., 151 pages. Price $14 00

This monograph is well written, concise, clinically oriented and nicely illustrated with simple diagrams and carefully selected tracings. It is short but all inclusive for the practicing cardiologist. The heart sounds, both normal and abnormal, are oriented properly with hemodynamic phenomena The book consists of nine chapters devoted to apparatus and technique and to the physics of the heart sounds and murmurs. The author an authority on the subject, has considered the important and common auscultatory problems of the normal and diseased heart This is an excellent and well-organized book which is highly recommended to all clinicians and students.

RESPIRATION AND CIRCULATION Edited by Philip L. Altman and Dorothy S. Dittmer Bethesda, Md 1971 Federation of American Societies for Experimental Biology 930 pp. Price $30.00.

This volume of the Handbooks of the Federation of American Societies for Experimental Biology is another excellent addition to those already published. The sponsors are to be congratulated and thanked for this effort and service to biology and medicine. As was true of the previous volume, the contributors are numerous, they are experts in their respective fields, and the material covered is fairly complete and authoritative. This volume is too extensive for a detailed review Anyone who can afford to own not only this volume but the entire series should do so. Like the *Encyclopedia Britannica* these handbooks should be on the reference shelf of all physicians and biologists. Another excellent volume is now available.

CARDIOVASCULAR CLINICS—ARRHYTHMIAS, Vol. 4 No. 2 Edited by Leonard S. Dreifus, M.D Philadelphia, 1970 F A. Davis Company 313 pp. Price $10.00.

This is another good issue of *Cardiovascular Clinics*. Dreifus has gathered together several important practical aspects of cardiac arrhythmias which confront the clinician on a regular basis. The authors of the 16 rather short but concise and clearly written contributions have kept the physician and patient in mind. The discussions of mechanism diagnosis, and management are consistent with current considerations. A V block, tachycardia, Stokes-Adams syndrome, pre-excitation syndrome, A V nodal rhythms, pacemaker arrhythmias, and the use of drugs and electric cardioversion are discussed This is another good publication. The introduction of the series of *Cardiovascular Clinics* is welcomed by this reviewer

KIDNEY DISEASE IN THE YOUNG. By Elvira Goettsch, M D based on studies carried out in collaboration with the late John D Lyttle, M D Philadelphia, 1971 W B Saunders Company 305 pp. Price $22.50.

This important book on kidney disease in the young should interest all doctors. Many patients with advanced chronic or terminal renal disease in adult life begin with unrecognized and neglected renal disease in childhood. Were renal disease diagnosed in their youth and proper therapy initiated ma y of these people would not die of renal insufficiency in later life. The importance of early diagnosis and early management is well known b t till neglected Goettsch book is fairly comprehensive, consisting of six parts and 70 chapters, each usually of two to three pages in length. The parts include Bright s disease in childhood acute glomerulonephritis, nephrotic syndrome common forms of chronic glomerulonephritis, chronic pyelonephritis, and less com m n forms of Bright disease. Readers will take exception to certain aspects of any book like this. For example, on page 21 the author tates that cl mate is without effect on glomerulonephritis. This may be true, b t the statement is based on only one study However he fails to tate that the disease is more common i its acute form when upper respiratory and related infections are more common, as in the winter months of the temperate zone. However glomerulonephritis is

encountered in warm areas of the world which earlier writers failed to realize. Goettsch has produced a book which really consists of a series of short papers. From the undergraduate student standpoint this book lacks chapters concerning the normal kidney, classifications and diagnosis of renal disease, methods for study and definition of renal function, basic principles of normal and abnormal renal physiology and pathology, details of urinalysis, and basic principles in therapeutics. Those who are well informed in such matters will find this to be a useful book.

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Books received

THE BATTLE AGAINST HEART DISEASE. By P E. Baldry M B., B.S. M R.C.P., New York, 1971 Cambridge University Press 189 pages. Price $10.00.

BLOOD CELLS AS A TISSUE Edited by W L. Holmes, Ph.D New York and England 1970 Plenum Publishing Corporation 371 pages. Price $15 00.

CARDIOVASCULAR NURSING. By Jeanette Kernickl, R.N., M.S. Barbara Bullock R.N B.S. and Joan Matthews, R.N., B.S. New York 1971 G P Putnam's Sons, 431 pages. Price $9 75

CARDIOVASCULAR SURGERY Ed 2. By Ormand C. Julian M D Ph D., William S. Dye, M D., Hushang Javid M D Ph D James A. Hunter M D and Hassan Najafi M D Chicago, 1970, Year Book Medical Publishers, Inc. 365 pages. Price $13.50.

CORONARY HEART DISEASE IN SEVEN COUNTRIES. Edited by Ancel Keys, Ph D New York, 1970, The American Heart Association, Inc., 211 pages. Price $5.00.

CURRENT THERAPY—1971 Edited by Howard F Conn, M D Philadelphia 1971 W B Saunders Company 836 pages. Price $16.00.

ELECTRONIC INSTRUMENTATION THEORY OF CARDIAC TECHNOLOGY By Laurence W Piller Springfield, Ill., 1971 Charles C Thomas, Publisher 224 pages. Price $12.50.

HEALTH SCIENCES IN ISRAEL (INSTITUTIONS AND SCIENTISTS) Edited by Betty Dawes, Jerusalem, 1971, Israel Journal of Medical Sciences, 285 pages. Price $7 00.

THE HEART AND ITS ACTION ROENTGENKYMOGRAPHIC STUDIES. By Gilbert H Alexander M D., St. Louis, 1970 Warren H Green, Inc., 259 pages. Price $22.50.

THE HISTORY OF CORONARY HEART DISEASE. By J O Leibowitz M D Berkeley—Los Angeles—New York, 1971 University of California Press, 235 pages. Price $8.50.

HYPERTENSIVE MECHANISMS, PROCEEDINGS OF A CONFERENCE HELD IN CANBERRA, AUSTRALIA, IN 1970. Edited by Ralph Reader D Phil. F R.A.C.P M R.C.P., New York, 1970 The American Heart Association Inc. 289 pages. Price $6.00.

ANAESTHESIE IN DER HERZCHIRURGIE. By Ruth Gattiker Berne Switzerland, 1971 Hans Huber Publisher 259 pages.

RISK. By Rachel MacKenzie, New York, 1971 The Viking Press Inc. 59 pages. Price $3.95.

THE ANATOMY OF AGING IN MAN AND ANIMALS. By Warren Andrew New York and London, 1971 Grune & Stratton Inc. 259 pages. Price $15 00.

Announcements

International symposium on arrhythmias

An international symposium on recent advances in cardiac arrhythmias will be held in Amsterdam, The Netherlands, on March 23 and 24 1972.

For further information, write to Dr D Durrer University Department of Cardiology and Clinical Physiology Wilhelmina Gasthuis, le Helmersstraat 104 Amsterdam, The Netherlands.

AAMC Annual Meeting

Prepaid medical care, health maintenance organizations, financing of health services, and training and use of allied health personnel will be the featured topics at the 22nd Annual Meeting of the American Association of Medical Clinics, to be held September 14-18, 1971 at the Sheraton-Cleveland Hotel, Cleveland, Ohio.

G Stanley Custer M.D AAMC President, has issued an invitation to non member physicians in group practice, as well as others interested in group practice to attend the meeting. Prospective non member attendants may secure further information by contacting AAMC, 719 Prince St., Alexandria, Va. 22313.

American Heart Journal

Sept., 1971 Volume 82 Number 3

Editorial

Progeria of Hutchinson-Gilford: A caricature of aging

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Franklin L. DeBusk, M.D.
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Gilford[1] summarized Hutchinson's[2,3] and his own observations as follows in coining the term "progeria" to replace his earlier suggestion of "micromegaly."[4] This latter term, a classical etymological blunder, reflected his concept of this disorder being of pituitary origin and the opposite of acromegaly.

> Two cases of a peculiar and strongly featured disease have been described . . . the disorder began without apparent cause, and was characterized by a curious mixture of immature development . . . and of premature old age. . . . They died apparently from senile decay, one at the age of 17, another at 18. . . . In stature they were children, but in other respects they looked like old men. They were lean, weak, decrepit and bald. . . . Their skins were dry, wrinkled and wasted and did not conceal the underlying tendons and veins.
>
> A postmortem examination was made on one of them and the same extraordinary mixture of youth and of advancing old age was found to characterize the various internal organs. There was a large healthy liver and slightly degenerated kidneys and suprarenal bodies. The brain was healthy. . . . There was a persistent and degenerated thymus gland. The thyroid, pituitary and pineal bodies appeared to be healthy. . . . There was marked atheromatous and calcareous degeneration of the coronary arteries, aorta and valves of the left side of the heart.
>
> The name progeria (*progeros*, prematurely old) has been given in recognition of the senile characters which form such a conspicuous feature of the disease from the beginning.

The clinical features of Hutchinson's two original cases have been repeatedly observed with remarkable lack of variation. DeBusk[5] has been able to confirm 59 cases from the world literature while excluding a number of duplications and probable examples of cleidocranial dysostosis, Hallermann-Streiff syndrome, and progeroid syndromes. Despite the great specificity of the Hutchinson-Gilford progeria syndrome (HGPS), many reports contain insufficient description for confirmation of the diagnosis or describe other syndromes.

The course is an inexorable and progressive one characterized by loss of subcutaneous fat, growth failure, osteoporosis, joint stiffness, total alopecia, and thinning of the skin. Atherosclerotic changes become important in the first decade of life with the development of angina, congestive heart failure, hypertension, occasional cerebral vascular accidents, and myocardial infarctions.

In twenty reported cases, the age and circumstances of death are known and in nine cases necropsy data are available. Age at death varied from 7 to 27½ years with a median of 12 and a mean of 13.4 years. Two brothers died of "marasmus and inanition" and one girl with convulsions.

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Two patients died from head injuries The remaining 15 children died either of congestive failure due to previous infarction or of acute myocardial infarction

Most of the autopsied patients have had patchy and focal myocardial fibrosis and necrosis rather than typical acute infarction[7] Coronary and aortic atherosclerosis is usually extensive and calcification is commonly seen in the coronary arteries and aortic valves. Nephrosclerosis has been described in seven cases.[8] The accumulation of lipofuscin deposits in the brain adrenal cortex kidney testes liver and heart has been described in a report of two patients said to have progeria but no confirmatory descriptive information is given[7] This pigment is a highly oxidized lipid with characteristic fluorescence which accumulates as a function of age It is rarely seen in normal children or adolescents.

There is some doubt whether the myocardial changes are circulatory[7] Hyperlipidemia has not been consistent nor marked when present Serious myocardial disease has been noted without significant coronary arterial occlusive disease and intramural branches of the coronary arteries have been free of pathologic changes. A generalized disorder of connective tissue is indicated by the finding of fibrosis in sites other than myocardium including the skin and periarticular tissues

Further evidence of mesenchymal dysplasia has been described in vitro Fibroblast cultures from the skin of a 9 year-old patient survived only two subcultures in contrast to 20 to 30 subcultures in age matched controls.[9] We have twice failed to establish skin fibroblast cultures from a patient with HGPS The incorporation of labeled glucose and proline into skin and bone was markedly depressed in two patients studied by Villee and associates.[10]

A number of features of true senility are not seen in progeria and certain aspects of the phenotype (e.g total alopecia mandibular hypoplasia) are not characteristic of aging These children do not develop progressive senile brain disease Rosenbloom and associates[11] have recently described electroencephalographic patterns during sleep which were consistent with the patient's chronological age. The joint limitation in HGPS is apparently due to periarticular fibrosis rather than senile osteoarthritis.

Extensive metabolic investigation has not clarified the defect in HGPS Mitochondrial oxidative function has been described[10] and is consistent with scattered reports of elevation in basal metabolic rate This likely represents the greater metabolic activity needed in a person without the thermal insulation of subcutaneous fat. Growth hormone responses were thought to be deficient but have now been shown to be normal[11, 12] A consistent finding that resembles the aging state is a degree of insulin resistance manifested by excessive tolerance to tolbutamide and injected insulin and elevated resting levels of immunoreactive insulin in the plasma.[11-13] These abnormalities have not been associated with glucose intolerance

Studies of the mechanics of skin collagen from two patients have been described.[14] They had a higher shrinkage temperature at both low and high loads than normals. On cooling the collagen from the patients, the material again extended to its original length Collagen from normal children and adults did not show this reversal

The morphological and metabolic observations in HGPS are consistent with a constitutional dysplasia of mesenchymal tissue The precise nature of the defect and how it leads to the cardiovascular and other changes are part of a mystery containing potential clues to solve the riddle of aging Changes in vessel walls due to inborn and acquired factors impairing the metabolism of structural proteins might lead to atherosclerosis and coronary artery disease

In the three quarters of a century since the Hutchinson-Gilford progeria syndrome was first described little has been added to the essential recognition of the curious mixture of immature development and of premature old age Despite more sophisticated analyses of these fascinating patients the secret of their mesenchymal dysplasia remains as safe as that of the process it caricatures.

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Clinical communications

Double outlet right ventricle with left ventricular outflow tract obstruction due to small ventricular septal defect

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When both great arteries originate from the right ventricle[1-3] a ventricular septal defect almost always is present and this defect constitutes the left ventricular outflow tract—the only exit from the left ventricle Usually the ventricular septal defect is large enough to permit unimpeded left ventricular ejection Occasionally however the ventricular septal defect can be small resulting in left ventricular outflow tract obstruction Although only six such cases have been documented previously[3-8] to our knowledge widespread awareness of this uncommon anomaly appears desirable because double outlet right ventricle with left ventricular outflow tract obstruction can be corrected by open heart surgery[8]

The principal purposes of this paper are (1) to report the second patient with this anomaly who is known to have been successfully corrected surgically and (2) to clarify further the pathologic anatomy of this malformation based on one autopsy case

Case 1

A 5-year-old white boy was referred to the Montreal Heart Institute with the history of a normal gestation and birth. On the tenth day of life, a systolic heart murmur was first heard During the first year growth and development were considered normal. Subsequently however dyspnea, frequent respiratory infections, intermittent cyanosis, and occasional squatting appeared He was hospitalized in Bolivia and then referred to the Montreal Heart Institute.

Physical examination The physical examination revealed a well-developed well nourished acyanotic 5-year-old boy in no distress. Peripheral pulses were normal and blood pressure was 90/50 mm Hg A systolic thrill, Grade III/IV was palpable along the left sternal border in the suprasternal notch and

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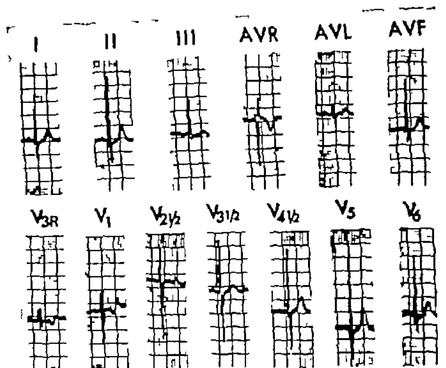


Fig. 1 ECG, Case 1.

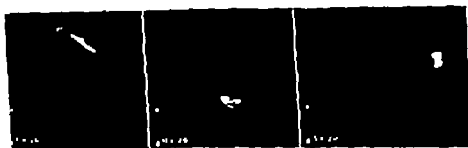


Fig. 2 Vectorcardiogram, Case 1 (retouched). The leftward, posterior and inferior QRS forces suggest left ventricular hypertrophy

over both carotid arteries. The second heart sound was single, and third sound was present at the apex. A harsh pansystolic murmur Grade IV/IV was heard along the left sternal border maximal at the fourth interspace. A shorter systolic murmur was heard t the upper right and left sternal borders, radiating to both carotid arteries.

Electrocardiography The electrocardiogram (ECG) showed mean frontal QRS axis of 60° (Fig. 1) and suggested left ventricular hypertrophy probably ith right ventricular hypertrophy also. Vector cardiography (Fig. 2) confirmed the impression of left ventricular hypertrophy

Chest roentgenogram. X-ray of the chest (Fig. 3) revealed mild cardiomegaly (cardiothoracic ratio, 9.5/18 53 per cent) nd increased pulmonary vascularity Cinefluoroscopy showed hyperpulsatility of the pulmonary artery



Fig. 3 Chest roentgenogram, Case 1.

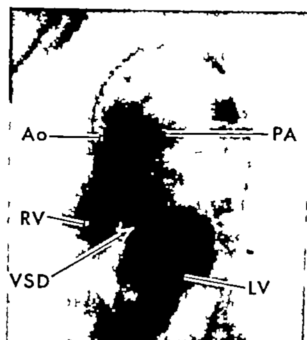


Fig 4 Cineangiocardiogram Case 1 following injection into left ventricle (*LV*) Smallness of the ventricular septal defect (*VSD*) was seen, followed by opacification of the right ventricle (*RV*) after which the aorta (*Ao*) and pulmonary artery (*PA*) were visualized simultaneously with approximately equal density of contrast

Cardiac catheterization Cardiac catheterization (Table I) revealed that the systolic pressures in the right ventricle pulmonary artery and aorta all were identical (systemic) Left ventricular pressure was suprasystemic there being a 74 mm. Hg peak systolic gradient between the left ventricle and the right ventricle beneath the aortic valve Although the left atrium was not entered the pulmonary artery wedge pressure was considerably elevated (27 mm. Hg) indicating left atrial hypertension. The pulmonary/systemic flow ratio was 4.3/1 0 (dye dilution curve) A patent ductus arteriosus was established by venous catheter passage

Cineangiocardiography This was performed by injection into the left ventricle via a retrograde arterial catheter (Fig 4) Opacification of the left ventricle was followed by visualization of the *small* ventricular septal defect The right ventricle then opacified rapidly followed by simultaneous visualization of the aorta and pulmonary artery Although the obstructively small ventricular septal defect appeared to be somewhat more subaortic than subpulmonary (Fig 4) the oxygen saturation in the pulmonary artery and in the aorta were nearly identical (93 and 95 per cent respectively Table I) Hence the oxygen data provided almost no evidence of preferential streaming of saturated left ventricular blood into the aorta Aortic root injection revealed that the patent ductus arteriosus was large

Operation At operation it was found that the aorta and pulmonary artery both originated from the right ventricle The septal band was hypertrophied but normally formed The obstructively small slit like ventricular septal defect (VSD) measured 6 by 2 mm from the right ventricular aspect and was much closer to the aortic than to the



Fig 5 Postoperative left ventriculography via retrograde aortic catheter Case 1 revealing absence of VSD and stenosis of left ventricular outlet.

pulmonary valve A short cuff of subaortic conal muscle separated the aortic valve from the small VSD Excision of the subaortic conal muscle was carried out. This raised the "roof" of the VSD, thereby enlarging the defect that served as the sole left ventricular outflow tract. The enlarged VSD then measured 2.5 by 3 cm. The defect was closed with a teflon patch that was sutured to the right of the aortic annulus, restoring virtually normal hemodynamics left ventricle 105 mm. Hg ascending aorta 100 mm. Hg and right ventricle, 35 mm. Hg On the fifth postoperative day respiratory distress necessitated tracheostomy Aside from subglottic stenosis requiring tracheoplasty the child recovered well and is now entirely asymptomatic.

Repeat cardiac catheterization Seventeen months postoperatively (Table I) a repeat cardiac catheterization disclosed no shunt by dye dilution curves, mild elevation of the right ventricular systolic pressure (41 mm Hg) a trivial pulmonary outflow tract gradient (9 mm Hg) a normal pulmonary artery wedge pressure (10 mm Hg) and complete abolition of the left ventricular outflow tract gradient Left ventriculography (Fig 5) confirmed absence of subaortic narrowing and absence of residual VSD

Case 2

This 9-month-old white female infant was born at term following an uncomplicated pregnancy and delivery A heart murmur was first detected at 5 days of age

Physical examination Examination at 5 days of age showed a vigorous and well-appearing 8 pound infant without cyanosis and with normal peripheral pulses, a normal first heart sound a normally split second heart sound, and a Grade II III/VI systolic ejection murmur along the left sternal border maximal at the third and fourth intercostal spaces.

Table I Catheterization findings Case 1

	Preoperative		Postoperative	
Site	O_2 saturation (%)	Pressure (mm. Hg)	O_2 saturation (%)	Pressure (mm. Hg)
SVC*	75		69	
IVC	85		66	
RA		(7)†	77	(6)†
RV in	81		75	41/2-6
RV out	82	100/8-11	75	
MPA	93	100/60	73	3 /13
PA wedge		27		10
LV		174/8-10		92/5-7
RV subaortic		100/10		
Ao	95	100/76	93	92/61
	$Qp/Qs = 4.3/1$ (dye curve) $Rp/Rs = 0.2/1$		$Qp/Qs = 1/1$ (dye curve) $Rp/Rs = 0.3/1$	

*Abbreviations: Ao, aorta; IVC, inferior vena cava; LV, left ventricle; MPA, main pulmonary artery; PA, pulmonary artery; Qp, pulmonary blood flow; Qs, systemic blood flow; RA, right atrium; RV, right ventricle; Rp, pulmonary vascular resistance; Rs, systemic vascular resistance.

†Mean pressures are in parentheses.

Table II Catheterization findings Case 2

Site	O_2 saturation (%)	Pressure (mm. Hg)
SVC*		
IVC	30	
RA mid	30	
RV in	33	
LPA†	40	(8)
Descending Ao	66	100/10
LPA → RV out → RV in	56	40 20
		80/43
		40/20 → 43/3 → 80/10

Qp/Qs 0.88/1.0.

*Abbreviations: See footnote to Table I.

†LPA, left pulmonary artery.

At 6 weeks of age a thrill was palpable in the left fourth intercostal space parasternally and the systolic ejection murmur had increased in intensity to Grade IV/VI. The ECG (Fig. 6) showed a mean frontal QRS axis of 95° and suggested biventricular hypertrophy predominantly right. The chest x-ray (Fig. 7 A) revealed mild cardiomegaly (cardiothoracic ratio, 7.5/12.3, 61 per cent) and the pulmonary vascularity appeared somewhat increased.

By 4 months of age, poor weight gain was evident (11 pounds 4.5 ounces). Physical findings were unchanged but the ECG (Fig. 6) suggested increasing left ventricular hypertrophy. During the next 5 months, episodes of intermittent cyanosis appeared.

At 9 months of age the infant was admitted to the Hartford Hospital in severe congestive heart failure. Physical examination showed flaring of the alae nasi, intercostal and subcostal retractions, generalized cyanosis, and hepatomegaly (4 cm. below the right costal margin). Auscultatory findings were unchanged except that the second heart sound was now single. The chest x-ray (Fig. 7 B) showed marked cardiomegaly (cardiothoracic ratio, 11.8/15.4, 77 per cent) and somewhat decreased pulmonary vascularity. The ECG (Fig. 6) now showed a right bundle branch block pattern and suggested increasing right ventricular hypertrophy.

Cardiac catheterization. This was performed after treatment with digitalis and diuretics (Table II). Pullback from the left pulmonary artery to the right ventricular inflow tract showed a 40 mm. Hg gradient at the ostium infundibuli. There was no pressure gradient between the right ventricle and the descending aorta. The pulmonary/systemic flow ratio was 0.88/1.0.

Angiocardiography. Following right atrial injec-

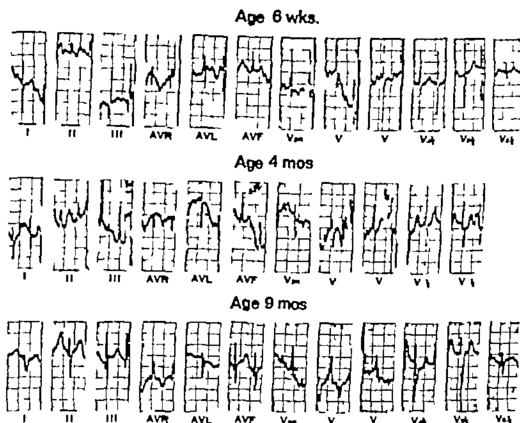


Fig. 6 Serial ECG's, Case 2.



Fig. 7 Chest roentgenograms, Case 2. *A*, 6 weeks. *B*, 9 months. Heart size increased and pulmonary vascularity decreased with age.

tion, angiocardiography (Fig. 8, *a*) showed origin of both great arteries from the right ventricle, stenosis of the pulmonary ostium infundibuli, bilateral (subpulmonary and subaortic) conus, and both semilunar valves at approximately the same height (pulmonary valve slightly higher than the aortic). Right ventriculography following retrograde aortic catheterization (Fig. 8, *b*) established that both great arteries originated side-by-side in approximately the same frontal plane.

The catheter was then advanced through a ventricular septal defect into the left ventricle and, at this point, the heart slowed markedly. It seemed probable that the ventricular septal defect was very small and that the catheter was largely or completely obstructing left ventricular egress. The catheter was quickly withdrawn and cardiac function was restored with the assistance of epinephrine and sodium bicarbonate. Left ventricular and pulmonary artery wedge pressures were not obtained. The operating room was readied for the creation of an atrial septal defect, but before the operation could be initiated cardiac arrest occurred and resuscitation was not possible.

Autopsy. The autopsy (Fig. 9) corroborated the diagnosis of double outlet right ventricle with severe left ventricular outflow tract obstruction, due to a remarkably small VSD that measured 0.3 by 0.3 cm. from the right ventricular aspect (Fig. 9,*b*). The smallness of the VSD was due to presence of

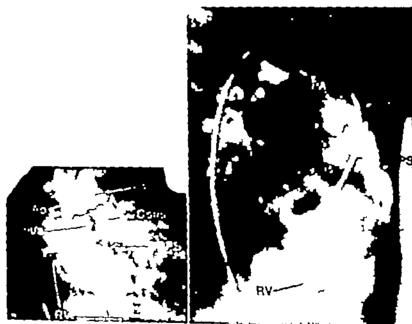


Fig. 9 Angiocardiography Case 2. *a*, Selective right ventricular cineangiocardiography showing origin of both great arteries from the right ventricle, with a bilateral *conus* (subaortic and subpulmonary) semilunar valves approximately at the same height (pulmonary slightly higher than aortic) and pulmonary infundibular stenosis (*PS*) at the os infundibuli. *b*, Right ventriculography via retrograde aortic catheter (right lateral projection, not simultaneous with *a*) showing stenosis of pulmonary os infundibuli (*PS*). The semilunar valves are approximately side-by-side (in almost the same frontal plane), the aortic valve (indicated by catheter in aorta) lying slightly anterior to the pulmonary valve (*PV*).

subaortic conal muscle (Fig. 9,*b*) that almost completely filled the space above the muscular ventricular septum. The size of the VSD was further reduced by a circumferential ring of endocardial sclerosis (jet lesion) about the rim of the defect on its left ventricular aspect (Fig. 9,*e*). The pulmonary ostium infundibuli (Fig. 9,*c* and *d*) was also very small (0.3 by 0.4 cm.) constituting pulmonary infundibular stenosis. The aortic infundibulum was not obstructive between the right ventricle and the aorta (Fig. 9,*b*) but it was very obstructive between the left ventricle on the one hand and the right ventricle and aorta on the other—by almost closing the VSD. Hence, in this sense, there was both pulmonary and aortic infundibular stenosis. Apart from the hypoplastic ostium infundibuli, the pulmonary infundibulum was well developed. The aortic infundibulum was less well developed, but there was 0.7 cm. or more of subaortic conal muscle separating the aortic valve from the anterior tricuspid leaflet. The coronary artery distribution was normal (Fig. 9,*e*) not as is typical complete *d*-transposition. Hypertrophy and enlargement of the left atrium and left ventricle (Fig. 9,*a* and *e*) were marked. The foramen ovale was obliquely probe patent, functionally closed, and the atrial septum bulged into the right atrium. The left ventricle displayed antemortem mural thrombi (Fig. 9,*e*).

Discussion

Double outlet right ventricle with left ventricular outflow tract obstruction was first described to our knowledge by Edwards, James, and DuShane[7] in 1952. The ventricular septal defect was completely closed by adherent mitral valve tissue in Edwards' case,[7] which is a different anomaly from that reported in the present paper.

Lauer, DuShane, and Edwards[8] in 1960 first reported the malformation shown by our two patients (Case 2[9]). In Lauer's case, a 13-year-old boy, the ventricular septal defect measured 0.4 by 0.6 cm., pulmonary infundibular and valvular stenosis was present, and an unsuccessful surgical attempt was made to enlarge the ventricular septal defect as part of reconstruction of the outflow tract from the left ventricle to the aorta with the use of a teflon channel. This is the same operation that was performed in Case 1.

In 1962, Cheng[4] reported a second example of this anomaly in a 21-year-old man, who had a 74 mm. Hg gradient between the left ventricle (156/4 mm. Hg) and the brachial artery (82/43 mm. Hg) measured simultaneously. In contrast to Lauer's case, pulmonary stenosis was not present.

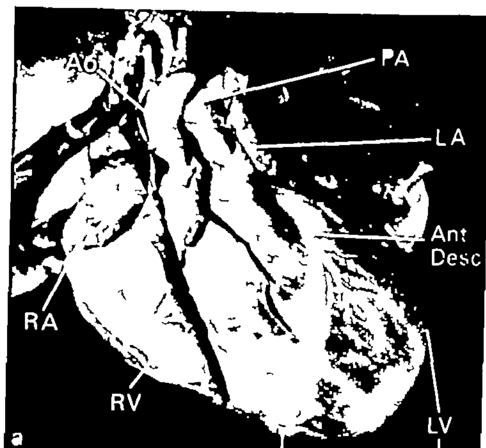


Fig. 9. a, Heart specimen, Case 2, exterior anteroposterior view. Both great arteries originate to the right of the anterior descending coronary artery (*Ant Desc*), accurately suggesting double outlet right ventricle. The aorta (*Ao*) and pulmonary artery (*PA*) arise at approximately the same height and side-by-side, accurately suggesting the presence of conal musculature beneath both semilunar valves. Much more left ventricle (*LV*) is visible in the frontal view than normally, reflecting very marked left ventricular hypertrophy and enlargement.

Cheng's patient[4] died 5 hours after selective left ventricular cineangiocardiography with the use of 70 per cent Urokon. This is strongly reminiscent of our patient (Case 2) who also died shortly after left ventricular catheterization via a small VSD. The hazards of this maneuver are obvious but the catheter may be passed through the defect before the diagnosis is clear. It should be added that a catheter was passed through a small VSD in our Case 1 without incident. Hence, we are not suggesting that a catheter should never be passed through a small VSD in this anomaly; rather, we seek only to emphasize that this can be a very risky maneuver.

Serratto and colleagues[5] in 1967 published three more well-documented cases of this anomaly (a 9-year-old boy, a 6 year-old boy, and an 11 year-old girl), bringing the total to 5 cases. Mason and associates[6] reported a sixth case, a 1? year-old boy, the first in whom surgical correction was successfully accomplished by an operation very similar to that in Lauer's Case 2[3] and in our Case 1.

Hence, our 2 patients bring the known total of well-documented cases of this anomaly to 8, and our Case 1 is the second patient with this malformation to have undergone successful surgical correction.

What produces left ventricular outflow tract obstruction? Or why is the VSD so small in this anomaly? Thus far, we have said that the smallness of the VSD *is due to the* presence of subaortic conal muscle (Fig. 9,*b*). This is part of the answer. Another important factor is the *alignment* of the conal musculature. If the conal musculature is in line with the muscular interventricular septum, then the conal myocardium will greatly reduce the space above the ventricular septum (the VSD). If abundant conal muscle is present but *not* appro-

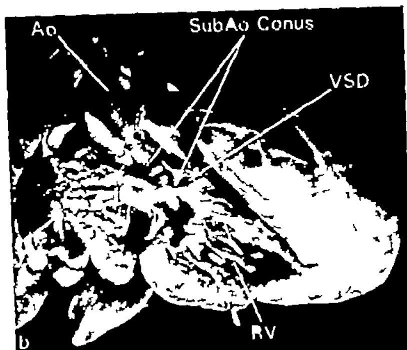


Fig. 9 b Case 2, opened right ventricle (*RV*) showing the obstructively small (0.3 by 0.3 cm.) ventricular septal defect (*VSD*) beneath the conal septum (*crista supraventricularis*) that separates the aortic and pulmonary outflow tracts. The *VSD* is neither subaortic nor subpulmonary but between (and beneath) these two valves (subcristal). It is the strategic location of this conal septum that lowers the "roof" of the *VSD* almost closing it, thereby obstructing the left ventricular outlet. The subaortic conus is seen. Note the jet lesion posterior-superior to the *VSD* in the subaortic conus.

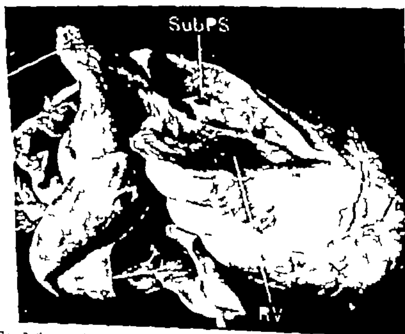


Fig. 9 (RV) Case 2, the stenotic pulmonary or infundibular (*Sub PS*) viewed from within the right ventricle

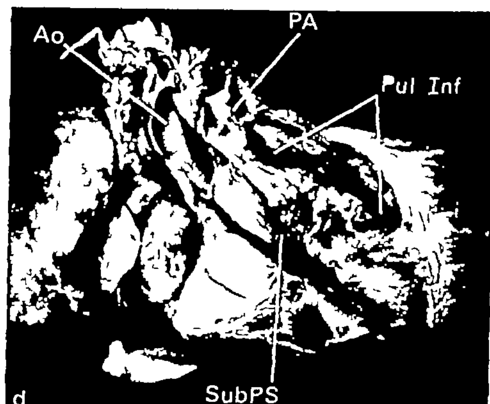


Fig 9 d Case 2 frontal view of the relatively capacious subpulmonary infundibulum (*Pul Inf*) and its stenotic os infundibuli (*Sub PS*)

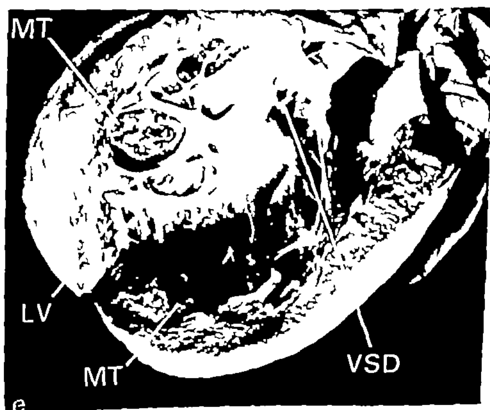


Fig 9 e Case 2, the markedly hypertrophied and enlarged *LV* The small *VSD* has been further narrowed by endocardial sclerosis about the rim of the defect on the *LV* side. Note the antemortem mural thrombi (*MT*).

priately aligned relative to the muscular ventricular septum then the VSD remains large—as in the Taussig Bing malformation. Hence, in the anomaly under consideration the VSD is small because of *appropriately aligned conal muscle*. In our Case 2 (Fig. 9) the conal musculature forming the "roof" of the VSD and making it very small is (1) the crista supraventricularis (parietal band) that lies almost sagittally and separates the pulmonary and aortic outflow tracts, best seen angiocardiographically (Fig. 8,*a*) and (2) the subaortic conal free wall posteriorly which lies beneath the posterior ("left") coronary leaflet of the aortic valve (Fig. 9,*b*).

From the surgical standpoint, since the conal musculature above the small high VSD contains no conduction tissue, it can be excised. Surgical VSD enlargement involves raising the "roof" of the defect: one cannot lower the "floor" (excise muscle of the interventricular septum) because of the conduction system.

Classification of double outlet right ventricle. We seek to focus attention upon this form with left ventricular outflow tract obstruction, that is omitted by all current textbooks, not only because it exists but also because it is currently correctable by open heart surgery. Based on the very limited available data, there may be a male preponderance in this anomaly: males, 6 and females, 2. This malformation is not confined to moribund infants. Indeed, it has presented most often in school-aged boys. The ages at death have ranged from 21 years to 9 months, with a mean of 9.7 years and a median of 10 years. The small high VSD is more subaortic than subpulmonary although the defect is not confluent with the aortic valve because of the interposed conal musculature (Fig. 9,*b*). Hence these cases of double outlet right ventricle may be classified as Type I of Neufeld, DuShane, and Edwards[1,2] or as partial transpositions in Lev's classification.[9] Pulmonary stenosis is a variable: it was present in five cases and absent in three.

In view of the foregoing, it is suggested that current classifications of double outlet right ventricle be amended to include this type with left ventricular outflow tract stenosis.

Summary

This is a report of the seventh and eighth known cases of double outlet right ventricle with left ventricular outflow tract stenosis due to a small ventricular septal defect. Case 1 is the second patient with this uncommon anomaly who has undergone successful surgical correction by enlargement of the ventricular septal defect and reconstruction of the outflow tract from the left ventricle to the aorta by means of a teflon tunnel. Case 2 was studied at autopsy and illustrates well the anatomic features of this malformation. It is suggested that this type with left ventricular outflow tract stenosis be incorporated into current classifications of double outlet right ventricle.

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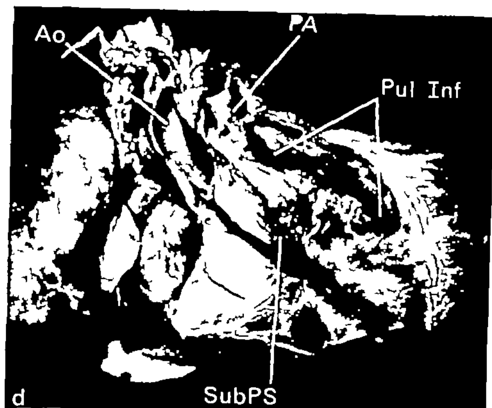


Fig 9 d Case 2 frontal view of the relatively capacious subpulmonary infundibulum (*Pul. Inf*) and its stenotic os infundibuli (*Sub PS*)

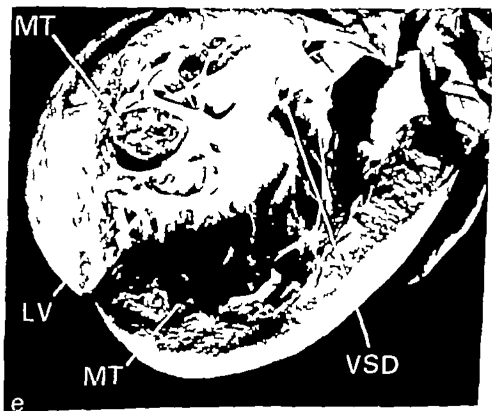


Fig 9 e Case 2, the markedly hypertrophied and enlarged *LV* The small *VSD* has been further narrowed by endocardial sclerosis about the rim of the defect on the *LV* side. Note the antemortem mural thrombi (*MT*)

Table 1 Hemodynamic, ECG, and clinical data from 26 patients with SVAS

Case No.	Age (years)	Peak systolic gradient (mm. Hg)	Peak systolic left ventricular pressure (mm. Hg)	ECG: Left ventricular hypertrophy	ECG: Strain	ECG: QRS-T angle frontal plane (degrees)	ECG: Right ventricular hypertrophy	SVAS syndrome	Associated cardiac defects	Cardiovascular symptoms	Surgery
1	20 mo.	10	126	—	—	30	+	+	Mild PPAS	—	—
2	7	10	120	—	—	5	—	+	—	—	—
3	10	13	75	—	—	30	—	+	PPAS, mild mitral insufficiency, hypoplastic right pulmonary artery	—	—
4	3	20	125	±†	—	40	—	—	—	—	—
5	5½	35	128	±	—	5	—	—	—	+	—
6	11½	35	158	—	—	55	—	—	—	—	—
7	8	36	138	±	—	20	—	—	—	—	—
8	4	39	135	±	—	15	+	MR‡	Mild pulmonic stenosis, PPAS, small PDA	—	—
9	29	44	168	+	+	20	—	—	—	++	—
10	13	46	176	+	+	90	—	—	—	++	+
11	½	50	160	—	—	50	—	—	—	—	—
12	30	52	166	—	—	20	—	MR	—	+++	—
13	5	56	212	±	—	60	—	—	—	+	+
14	13	58	200	—	—	10	—	—	—	++	+
15	3	60	160	—	—	30	—	+	Hypoplastic right and left pulmonary arteries	—	—
16	11	72	175	+	+	145	—	—	—	++	+
17	6	76	184	+	+	30	—	MR	—	—	—
18	14	78	247	+	+	180	—	+	—	++	+
19	5	80	190	+	+	215	+	—	Pulmonic stenosis, mitral insufficiency	—	+§
20	12	93	200	—	—	90	—	Mild MR	—	—	+
21	11	100	250	+	—	40	—	—	Mild VAS‖	—	+
22	3	110	250	+	+	110	—	—	—	+++	+
23	18	117	205	+	+	165	—	—	—	+++	+
24	9	117	189	+	—	75	—	—	—	+++	+
25	15	165	75	+	+	135	—	—	Mild VAS¶	++	—#
26	29	173	293	+	+	80	—	—	—	+++	+

PPAS, peripheral pulmonary artery stenosis.
†± suggestive of.
‡Mental retardation without other clinical manifestations of SVAS syndrome.
§Patient died at surgery. Autopsy confirmed SVAS with dilated coronary arteries and patchy thickening of the intima, healed apical myocardial infarct, and aneurysm.
‖Valvular aortic stenosis with peak systolic gradient 18 mm. Hg.
¶Valvular aortic stenosis with peak systolic gradient 19 mm. Hg.
#Patient lost to follow-up; it is not known whether surgery was performed.
**Patient died at operation. Autopsy confirmed diagnosis of SVAS; the coronary arteries were enormously dilated but atheromatous intimal plaques caused some narrowing of the arterial branches.

The electrocardiogram in supravalvular aortic stenosis

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There has been much interest in various aspects of supravalvular aortic stenosis since the early report of it by Denie and Verheugt[1] in 1958 Recent observation of a child with this condition who exhibited a normal electrocardiogram (ECG) in the presence of marked left ventricular hypertension prompted us to investigate the ECG characteristics of the malformation

The scalar ECG has been useful clinically in the evaluation of valvular aortic stenosis[2] although its limitations especially in comparison with vectorcardiographic techniques for the assessment of left ventricular hypertrophy have been increasingly emphasized[3,4] Its value in predicting the degree of obstruction in supravalvular aortic stenosis (SVAS) or in differentiating valvular from supravalvular stenosis has not been defined In addition the fact that the coronary arteries in supravalvular stenosis originate proximal to the site of left ventricular outflow obstruction and are probably exposed to elevated intraluminal pressures (in contrast to the situation in valvular aortic stenosis in which the coronary ostia are distal to the obstruction) suggested that comparative analysis of T wave morphology in the two conditions might represent an opportunity to evaluate clinically the influence of coronary artery perfusion pressures on myocardial repolarization

For these reasons and because no systematic study of the ECG in SVAS could be found in the literature the following series of patients is presented

Method

Twenty six patients with SVAS were assembled with the collaboration of seven California medical centers* Ages ranged from 20 months to 30 years Fourteen patients were men and 12 women All patients underwent left heart catheterization entry into the left ventricle by either retrograde arterial approach or by transthoracic puncture was successful in all but 2 patients Complete right heart catheterization was performed in 20 patients. Each patient had a 12 lead ECG at or near the time of cardiac catheterization The peak

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*Stanford University Medical Center Stanford: Patients 10 14, 16, 21 and 24; University of California Medical Center San Francisco Patients 2, 4, 5, and 20; Presbyterian Medical Center San Francisco Patients 6 7 12, 17 18, 23 25, and 26 University of California Medical Center Los Angeles Patients 15 and 19 Sutter Community Hospitals, Sacramento Patients 9 11 and 22; Children Hospital Medical Center Oakland Patients 1 3, and 13; Santa Clara Valley Medical Center San Jose Patient 8

Table I Hemodynamic ECG ...

Case No.	Age (year)	Peak systolic gradient (mm. Hg)	Peak systolic left ventricular pressure (mm. Hg)	ECG: Left ventricular hypertrophy	ECG: Strain	ECG: QRS-T angle frontal plane (degrees)	ECG: Right ventricular hypertrophy	SVAS syndrome	Associated cardiac defects	Cardiovascular symptoms	Surgery
1	20 mo.	10	126	—	—	30	+	+	Mild PPAS*	—	—
2	7	10	120	—	—	5	—	+	—	—	—
3	10	13	75	—	—	30	—	+	PPAS, mild mitral insufficiency, hypoplasia right pulmonary artery	—	—
4	3	30	125	±†	—	40	—	—	—	—	—
5	5½	35	128	±	—	5	—	—	—	+	—
6	11½	35	158	—	—	55	—	—	—	—	—
7	8	36	138	±	—	20	—	—	—	—	—
8	4	39	135	±	—	15	+	MR‡	Mild pulmonic stenosis, PPAS, small PDA	—	—
9	29	44	168	+	+	20	—	—	—	++	—
10	13	46	176	+	+	90	—	—	—	++	+
11	2½	50	160	—	—	50	—	—	—	—	—
12	30	52	166	—	—	20	—	MR	—	+++	—
13	5	56	212	±	—	60	—	—	—	+	+
14	13	58	200	—	—	10	—	—	—	++	+
15	3	60	160	—	—	30	—	+	Hypoplasia right and left pulmonary arteries	—	—
16	11	72	175	+	+	145	—	—	—	++	+
17	6	76	184	+	+	30	—	MR	—	—	—
18	14	78	247	+	+	180	—	+	—	++	+
19	5	80	190	+	+	215	+	—	Pulmonic stenosis, mitral insufficiency	—	+§
20	12	95	200	—	—	90	—	Mild MR	—	—	+
21	11	100	250	+	—	40	—	—	Mild VAS∥	—	+
22	3	110	250	+	+	110	—	—	—	+++	+
23	18	117	205	+	+	165	—	—	—	+++	+
24	9	117	189	+	—	75	—	—	—	+++	+
25	15	165	275	+	+	135	—	—	Mild VAS¶	++	—#
26	29	173	293	+	+	80	—	—	—	+++	+

*PPAS, peripheral pulmonary artery stenosis.
†± suggestive of
‡Mental retardation without other clinical manifestations of SVAS syndrome.
§Patient died at surgery. Autopsy confirmed SVAS with dilated coronary arteries and patchy thickening of the intima, healed apical myocardial infarct, and aneurysm.
∥Valvular aortic stenosis with peak systolic gradient 15 mm. Hg.
¶Valvular aortic stenosis with peak systolic gradient 19 mm. Hg.
#Patient lost to follow-up; it is not known whether surgery was performed.
**Patient died at operation. At operation confirmed diagnosis of SVAS; the coronary arteries were enormously dilated but atheromatous intimal plaques caused some narrowing of the arteria branches.

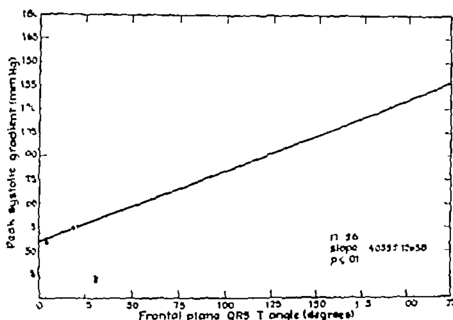


Fig. 1 Relationship between frontal plane QRS-T angle and the peak systolic gradient in 26 patients with SVAS. The correlation coefficient is 0.5472.

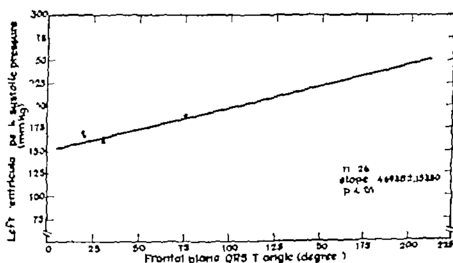


Fig. 2 Relationship between frontal plane QRS-T angle and the left ventricular peak systolic pressure in 26 patients with SVAS. The correlation coefficient is 0.5196

systolic gradient across the left ventricular outflow tract and left ventricular peak systolic pressures were used as criteria of severity and were correlated with ECG findings. None of the patients was receiving digitalis or had evidence of myocarditis or electrolyte imbalance. Twelve patients had corrective surgery; 2 expired at operation.

ECG's were analyzed and the findings compared with standard normal values.[4-6] The ECG was described as showing *definite* left ventricular hypertrophy if the R wave voltage in V_5 and/or V_6 exceeded the ninety fifth percentile for age or if the ninety fifth percentile for age or if the S-T-segment depression and flat, diphasic or inverted T waves were present in the left precordial leads. The ECG was *suggestive* of left ventricular hypertrophy if the R wave voltage in V_5 and/or V_6 was between the ninetieth and ninety fifth percentile for age or if the sum of S_{V1} and R_{V5} exceeded 50 mm.

Left ventricular "strain" was defined as depression of the S-T segment and flat or diphasic T waves in the left precordial leads; this term is used only as a succinct means of indicating changes in the direction of repolarization forces in the horizontal plane independent of QRS characteristics and is not to be interpreted as

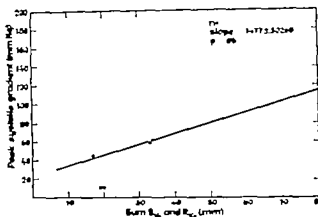


Fig. 3. Relationship between the sum of S_{V1} and R and the peak systolic gradient in 26 patients with SVAS. The correlation coefficient is 0.4223.

Table II. Incidence of left ventricular strain, abnormal frontal plane QRS-T angles, and left ventricular hypertrophy by voltage in relation to peak aortic systolic pressure gradient

Aortic peak systolic gradient	*No. of patients*	*Patients with left ventricular strain*	*Patients with wide QRS-T angles*	*Left ventricular strain or wide QRS-T angles*	*Patient with definite left ventricular hypertrophy by voltage*	*Patients with suggestive left ventricular hypertrophy by voltage*
> 70 mm. Hg	11	8	9	10	10	—
40-70 mm. Hg	7	2	2	1	2	1
< 40 mm. Hg	8	—	—	—	—	4

implying any specific type of structural or functional cardiac abnormality. The mean QRS-T angle in the frontal plane was determined in the usual way from the standard and unipolar leads.

Right ventricular hypertrophy was defined as an abnormally great R/S ratio and/or tall R wave in V_1,[4,5] or upright T waves in the right precordial leads in patients with normal S-T segments and T waves in V_4 and V_5.

Results

The relevant hemodynamic, ECG, and clinical data from the 26 patients in this study appear in Table I.

Analysis of these data shows that the peak aortic systolic pressure gradient and the peak left ventricular systolic pressure correlated about equally well with the QRS-T angle ($p < 0.01$). The sum of S_{V1} and R_{V} also statistically correlated with the peak aortic systolic pressure gradient but not as closely ($p < 0.05$). These relationships are depicted graphically in Figs. 1, 2, and 3.

The mean QRS vector in the frontal plane ranged from +10 to +95° with an average of +69°. T wave vectors in the frontal plane varied from +150 to −140° with an average of +12°. Eleven patients showed QRS-T angles of 60° or greater which were interpreted as abnormal.[7] All 11 patients with wide QRS-T angles had gradients greater than 45 mm. Hg and 9 had gradients exceeding 70 mm. Hg.

Table II categorizes the patients into 3 groups according to the magnitude of their peak aortic systolic pressure gradients and indicates the number in each group which displayed left ventricular strain, a wide QRS-T angle, and/or voltage criteria for left ventricular hypertrophy. Eight of 11 (73 per cent) patients with severe gradients (exceeding 70 mm. Hg) had ECG evidence of left ventricular strain. The 3 patients

(Nos 20 21 and 24) who had severe stenosis with upright T waves and normal S T segments in Leads V_5 and V_6 had gradients of 95 mm Hg 100 mm Hg and 117 mm Hg 2 of these 3 displayed voltage criteria for left ventricular hypertrophy and 2 had abnormally wide frontal plane QRS-T angles. Thus all patients with peak aortic systolic gradients of over 70 mm Hg manifested abnormality of at least one of the three ECG signs evaluated i e voltage criteria of left ventricular hypertrophy abnormally wide frontal plane QRS angle and left ventricular strain

Of the 7 patients with aortic peak systolic pressures between 40 and 70 mm Hg 4 had normal ECG s and 1 other had only suggestive voltage criteria for left ventricular hypertrophy

None of the 8 patients with pressure gradients of less than 40 mm Hg had left ventricular strain a wide frontal plane QRS-T angle or definite left ventricular hypertrophy by voltage Four had suggestive left ventricular hypertrophy by voltage criteria

Discussion

These findings show that the ECG characteristics in this group of patients with SVAS are similar to those of recent series of cases with stenosis at the valvular level (VAS) [1-4] There are statistically significant correlations between the severity of the stenosis and the ECG manifestations of left ventricular hypertrophy However again in common with other series there are frequent enough individual exceptions to make an estimation of the severity of aortic stenosis based on the ECG clinically risky As indicated by the results described in the text and summarized in Table II the observation of three ECG abnormalities (elevated voltage in V_5 and/or V_6 left ventricular strain and a wide frontal plane QRS-T angle) in combination seemed clearly to identify patients with severe left ventricular outflow gradients (over 70 mm Hg)—although there was one exception even in this group Patient 21 who was the original stimulus for this study—and to identify those with mild gradients (less than 40 mm Hg) The ECG s of patients in the middle group with gradients between 40 and 70 mm Hg could not be used reliably to predict the magnitude of the gradient

Hugenholtz and Gamboa[2] state that the resting ventricular peak systolic pressure is the dominant factor influencing the electromotive forces of the heart In our group of patients, the correlation between peak systolic left ventricular pressure and the frontal plane QRS-T angle was not significantly better than that between the peak systolic gradient and the QRS-T frontal plane angle. Clearly inclusion of enough additional data (particularly cardiac output at the time of the catheterization) for the calculation of valve areas would be helpful in providing a more complete hemodynamic profile and thus would permit more accurate categorization for comparative purposes. Although unfortunately this information was not available in a sufficient number of patients (who were evaluated retrospectively) to make precise analysis meaningful some semi-quantitative comments can be made Oxygen consumption was measured at the time of catheterization in only 4 cases but in all except 4 others cardiac output could be estimated by an assumed consumption. With the use of an intentionally wide range for normality of 3 0 to 5 0 L. per square meter Patients 2 5 6 and 14 had abnormally high outputs and Patients 3 19 and 23 had low outputs at the time of study On the basis of these calculations, then, only Patients 3 and 14 could be significantly misplaced in the listing of the order of lesion severity in Table I

One of the problems in comparing our results with those in a series of patients with valvular stenosis is the multiplicity of measurements used to estimate the severity of aortic stenosis and the even greater number of criteria of abnormality applied to electrocardiographic data [9] Admittedly our criteria were chosen arbitrarily different ones may have yielded more significant correlations although upon review they seem not to have in others reports. Gamboa Hugenholtz and Nadas,[3] however offer convincing evidence for the superiority of the corrected vectorcardiogram (Frank) to either the uncorrected cube system or the standard ECG in the assessment of

valvular aortic stenosis. Again unfortunately in our study there were too few vectorcardiograms available to permit meaningful conclusions to be drawn.

As indicated in the introduction one of the purposes of this investigation was to evaluate whether a difference in the incidence of abnormalities of repolarization over the left precordium in this group of patients (whose coronary arteries arose proximal to the site of stenosis and thus presumably were exposed to high perfusion pressures) compared with the incidence in patients with aortic valvular stenosis might provide clinical evidence for or against the theory of myocardial hypoxia as the pathogenic mechanism for these ECG changes. Linzbach[18] accepted myocardial hypoxia as a concomitant of what he called pathologic hypertrophy and concluded on the basis of his own observations and the work of others, that the main cause of this hypoxia was narrowness, in relation to heart size of the coronary ostia and larger arteries. He maintained that the fiber-capillary ratio was normal in this situation. The morphologic observations of Grimm Kubota and Whitehorn[19] in experimentally produced cardiomegaly seemed to provide support for Linzbach's theories. More recently however Kerr Bonner and Pilato[20] found that, in experimentally produced cardiac hypertrophy in rats, the myocardium did not outgrow its coronary blood supply.

It seemed to us that the frequent observation of large dilated proximal coronary arteries in SVAS provided an opportunity to add evidence for or against Linzbach's hypothesis. The relatively young age of our patients (only 3 were over 20 years of age) tended to eliminate the additional factor of arteriosclerotic causes of S-T T wave abnormalities frequently operative in older patients.

The lack of any significant difference between the incidence of abnormalities of repolarization in patients with SVAS and those with VAS suggests the conclusion that myocardial hypoxia is not the primary etiologic factor in the pathogenesis of the S-T T wave abnormalities of left ventricular hypertrophy. However three special considerations make an unqualified acceptance of this conclusion unwarranted.

1. No correlation between the size of the coronary ostia and proximal arteries and the volume of coronary blood flow has actually been demonstrated. In the normal heart there is a large range of possible flow rates[21] and it is reasonable to assume that at least some of the numerous normal physiologic determinants of flow are operative in diseased states as well.

2. The coronary artery hypertension presumed to be present in most of these patients may give rise to the chronologically premature development of medial hypertrophy, fibrous intimal thickening, and atherosclerosis[4, 13] which in some cases leads to localized areas of coronary constriction. A review by Peterson Todd and Edwards[4] describes such abnormalities of the coronary arteries in 20 of 33 patients with SVAS. Both patients in this study who expired demonstrated atherosclerotic or other intimal coronary changes at autopsy (Patients 19 and 26). Patient 19 was a 5-year-old child who had pathologic findings of patchy thickening of the coronary artery intima, a healed apical myocardial infarct, and a ventricular aneurysm.

3. The free margins of one or more aortic valve leaflets may adhere to the intima of the aorta at the level of the supravalvular obstruction[14,24] and result in compromised coronary filling by obstruction of the sinuses of Valsalva. None of the patients in this study was noted to have this anomaly at operation or autopsy.

The anatomic coronary and aortic leaflet abnormalities found in association with SVAS may account for differences between the incidence of ECG changes of left ventricular hypertrophy in coarctation of the aorta (where the site of obstruction also is distal to the origin of the coronary arteries) and SVAS. Brann for example found less frequent and less severe changes in a group with uncomplicated coarctation which were similar physiologically to a VAS group; this is at variance with our conclusions about the similarity between those with supravalvular versus valvular lesions.

Thus, this study while tending to support a nonhypoxic pathogenesis for the S-T T wave changes in left ventricular hypertrophy cannot be considered defini

tive More complete physiologic, vector cardiographic and pathologic information in a significantly larger series of patients with this entity might provide more significant correlations probably however a satisfactorily complete understanding of abnormalities of repolarization will depend upon experimental studies in animal models

Summary

Analysis of hemodynamic ECG and clinical data in 26 patients with SVAS shows an incidence of ECG abnormalities similar to that in comparable series of patients with VAS One or more of three ECG signs voltage criteria of left ventricular hypertrophy abnormally wide frontal plane QRS angle or left ventricular strain segregated patients with severe and mild left ventricular outflow obstruction but lack of correlation in the group with medium degrees of obstruction and individual exceptions in all three categories make the ECG a clinically unreliable means of assessing the severity of SVAS

The findings do not support the theory of myocardial hypoxia as the pathogenesis of abnormal S-T T wave changes in left ventricular hypertrophy However the unknown incidence in this group of patients of previously described coronary obstruction from adherent aortic valve leaflets or premature coronary intimal and medial thickening and the unavailability of actual coronary flow data make any definitive conclusion unwarranted

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Ventricular parasystole in healthy hearts

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Parasystole is defined as a dual rhythm wherein an ectopic pacemaker is in some way protected from the impulse of the sinus pacemaker.[1] It is considered a rare arrhythmia[2-4] in comparison to ventricular extrasystolic beats with fixed coupling and is furthermore presumed to denote underlying heart disease in the majority of cases.[2-4] It is the purpose of this communication to show that ventricular parasystole is a relatively common arrhythmia in apparently healthy individuals; also apart from diagnostic uncertainty (for long electrocardiographic strips are required) there seems to be little significance in distinguishing between ventricular extrasystoles and parasystole in otherwise normal individuals.

Material and methods

The data of this study were drawn from the analysis of electrocardiograms (ECG's) of 5,500 flying personnel examined regularly at the Military Medical Institute over the last 7 years. Annual resting and stress ECG's were available on all members over the age of 40, while biennial resting and at least one stress ECG were available on all members under the age of 40. Several individuals with ectopic beats were examined at yearly intervals and a continuous Holter audiovisual superimposed electrocardiographic presentation (AVSEP) magnetic tape recording was studied on 10 subjects. Rigid criteria were laid down for inclusion in the study, i.e., a detailed history and physical examination, retinoscopy, chest x-ray, blood pressure below 150 mm. Hg systolic and 90 mm. Hg diastolic, and a normal *resting* and *effort* ECG. The presence of uniform ectopic beats decreasing during exercise or occurring less frequently than one per 10 normal sinus beats was considered to be within normal limits.

All effort tests were performed in a supine position on a bicycle ergometer. Exercise continued until the pulse rate increased to at least 50 per cent above the resting value. A bipolar chest lead was recorded every minute during the total period of exercise and routine ECG leads were recorded on a multichannel recorder immediately and 5 minutes after exercise. The total period of exercise varied between 5 and 10 minutes in all individuals.

The tracings containing ectopic beats were analyzed with respect to normality, the presence or absence of ectopic beats and fusion beats, the coupling intervals between the ectopic beat and the preceding normal sinus beat, the configuration of the ectopic beats, and their relationship to exercise.

Parasystole was diagnosed when the coupling interval varied by 0.10 second or more during comparable sinus rates. The presence of fusion beats constituted addi-

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Table I

	Age groups (years)				
	16 to 25	26 to 35	36 to 45	46 to 55	56+
Total number of subjects	3 690	955	468	357	30
Total number of subjects with ventricular ectopic beats	36 (0 98%)	23 (2 41%)	20 (4 27%)	25 (7%)	1 (3 3%)
Number of normal subjects with ventricular ectopic beats	36 (0 98%)	22 (2 30%)	11 (2 35%)	12 (3 36%)	—
Number of normal subjects with ventricular parasystole	15 (0 41%)	11 (1 15%)	4 (0 85%)	7 (1 96%)	—

tional evidence of parasystole but was not essential in the diagnosis. According to the usual criteria i e constant observed or calculated shortest interectopic intervals and multiples thereof for longer interectopic intervals an attempt was made to calculate the individual parasystolic rates.

In subjects with occasional ectopic beats, or with ectopic beats in periodic tracings care was taken to measure the coupling intervals only during comparable sinus rates. Whenever doubt existed due to inadequate information ectopic beats were classified as ventricular extrasystoles.

Results

Ectopic beats were noted in 105 out of 5 500 subjects, i e 19 2 per 1 000 Twenty four of these were excluded from the study due to substantiated or probable cardiovascular disease (Table I)

The ages of the subjects ranged from 16 to 56 years Classification into the different age groups was made according to the youngest age at which ectopic beats were first noted (Table I)

Parasystole was present in 37 individuals fusion beats occurred in 22 of these A presumably accurate parasystolic rate could be calculated in 16 individuals. In these the parasystolic rate varied between 26 and 150 beats per minute with an average rate of 63 beats per minute varying degrees of exit block being present with the more rapid rates. In the other 21 individuals infrequent ectopic beats made calculation inaccurate and the diagnosis had to be assumed due to wide variation in coupling intervals which varied between 0 10 and 0 34 second

Discussion

Parasystole is recognized by the following three electrocardiographic signs[3] (1) marked variation in the coupling of the ectopic beats (2) regular appearance of the ectopic beats and (3) appearance of combination fusion or summation beats (mixed systoles)

Contrarily the only electrocardiographic sign to recognize true ventricular extrasystoles is fixed coupling between the ectopic beat and the preceding normal sinus beat. Although the criteria for differentiation between ventricular parasystole and extrasystoles are supposed to be simple and specific considerable difficulty is often encountered in individual cases. With routine 12 lead ECG s usually showing not more than 8 complexes per lead interpretation of the above parameters becomes inadequate

No consensus of opinion has been reached as to exactly how much variation in the coupling interval is permissible for it to be still considered fixed To complicate matters further cases of parasystole often reveal constant coupling notably when a simple mathematical relationship exists between the sinus rhythm and the parasystolic rhythm this coupling also may occur in retrograde conduction to the sinoatrial node leading to linkage of both rhythms in cases with a rapid [illegible]rate in

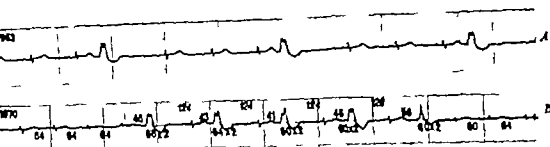


Fig. 1 A Lead V of 24-year-old pilot who was aware of an irregular heart beat for 11 years and who revealed multiple uniform extrasystoles with fixed coupling for 7 consecutive years. B Lead aV of the same individual depicting ventricular parasystole with rate of approximately 48 beats per minute. Subsequent magnetic tape monitoring revealed periods of extrasystoles with fixed coupling, periods of normal sinus rhythm, and periods of premature beats with varying coupling and fusion beats. During the latter period of presumed parasystole the attempted calculated parasystolic rate varied widely and unpredictably. In the figure the upper row of numbers represents the interectopic intervals, the middle row the coupling periods, and the lower row the normal RR intervals in hundredths of second.

which case there is no possibility for marked variations in coupling and when the parasystolic focus delivers subthreshold impulses that can stimulate the ventricles only during the supernormal phase of excitability. Also a well established parasystolic rhythm can suddenly and unpredictably change to true extrasystoles with fixed coupling and vice versa.

In the present study the diagnosis of ventricular extrasystoles made on routine examination was often changed to that of parasystole whenever long ECG strips became available (Fig. 1). The diagnosis of parasystole was made in 37 cases out of 81 in otherwise normal individuals with ventricular ectopic beats. It is quite possible that parasystole occurs even more commonly for in 21 out of the 44 individuals labeled as having ventricular extrasystoles, only a few premature beats were present for consideration.

An attempt was made to calculate the parasystolic rates in cases diagnosed as such. Although the exact parasystolic rate could be documented in several cases, this is the exception rather than the rule. When two ectopic beats appear consecutively measurement of this direct ectopic cycle is usually somewhat longer than those periods containing blocked discharges. The lack of numerical consistency is further complicated by several possible influences i.e. apparent spontaneous changes in parasystolic discharge rate and varying degrees of exit block (varying from delay[14] to typical Wenckebach[15] or 2:1, 3:1, 4:1, or even higher degrees of exit block.) Apart from the known unpredictable influence of carotid sinus stimulation[13-15] and exercise, several other still undefined factors might influence the parasystolic discharge rate.[16] This observation was confirmed with the present study (Fig. 2). Several of our cases with parasystole were monitored on an AVSEP magnetic tape for several hours. Although the parasystolic rate could not always be calculated confidently we were convinced of wide unpredictable variation in most, if not all, cases.

As far as fusion beats are concerned this only signifies that discharges from two independent pacemakers occur more or less simultaneously and it is obvious that in the presence of a long coupling interval, i.e. a premature beat occurring just prior to the next normal sinus beat, even slight variation in this interval may result in a fusion beat (Fig. 3).

On the basis of our results in this study and the discussion above, we are convinced that on a routine 12 lead ECG differentiation between ventricular extrasystole with fixed coupling and extrasystole with varying coupling or parasystole is often unrealistic. This is especially applicable to apparently healthy individuals. We agree with Lamb[17] and Surawicz and MacDonald that the guarded prognosis attached to the presence of ventricular parasystole was probably a reflection of the patient population studied. Even though the longest period of follow-up is only 7 years, we were impressed by the regular

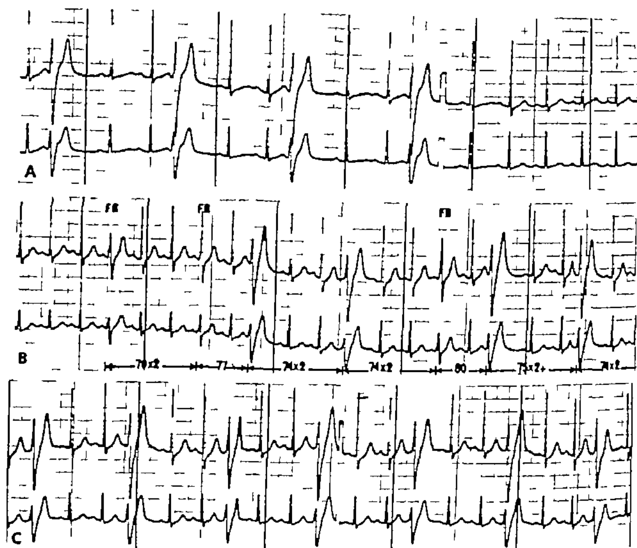


Fig 2 Simultaneous ECG strips of Lead V_1 and standard Lead II of a healthy 19-year-old man. *A* recording during rest. Ventricular ectopic beats with fixed coupling are present. Note postextrasystolic T wave changes. *B* and *C* continuous recording immediately after exercise The tracing shows an irregular ventricular parasystole with a rate varying between 75 and 86 beats per minute. The numbers between ectopic beats represent hundredths of a second Note also the marked variation in coupl ng intervals and three fusion beats (*FB*) In *C*, reversion to fixed coupling is evident. In this individual marked variation in coupling intervals also occurred after amyl n trite inhalation (not shown) Unfortunately the ECG roller slipped during the recording of the postexercise ECG as is evident from the narrow T waves of the third complex in *B* and the third ectopic beat in *C*. This, however does not invalidate the significance of the tracing

recurrence of ventricular premature beats and as far as could be ascertained that the beats probably originated from the same focus in each individual case This interesting observation is presently being investigated

In view of the fact that a distinction is usually drawn between ventricular parasystole and true ventricular extrasystoles it is to be expected that different mechanisms have been suggested for the individual arrhythmias However no concrete proof for the various mechanisms exists and it is not impossible that in many cases we have to do with different manifestations of the same arrhythmia In this context ventricular extrasystoles with varying coupling due to varying degrees of exit block could mimic ventricular parasystole. In regard to ventricular parasystole this study confirms Surawicz and MacDonald's[18] suggestion that the incidence of cases with irregular interectopic intervals which are not the product of the least common divisor increases in proportion to the lengths of the examined electrocardiographic strip

Summary

Parasystole was found in 37 out of 81 apparently normal individuals with ven

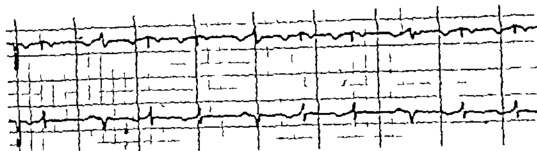


Fig. 3 Simultaneous strips of Leads V and V of 36-year-old healthy aviator The tracing depicts ventricular ectopic beats (complexes 3, 6, and 9) The coupling intervals between the preceding normal sinus beat and the ectopic beats are long, and it is evident that even slight variation in this interval results in varying degrees of fusion or combination between the ectopic and the subsequent normal sinus beat.

tricular premature beats. The diagnosis was made mainly on the basis of marked variation in coupling intervals while the presence of fusion beats in 22 cases and a plausible parasystolic rate in 16 cases provided additional but not essential evidence for the diagnosis. The problems encountered in the differentiation of parasystole from extrasystole with fixed coupling are discussed It is concluded however that such distinction is probably of limited significance in the patient population studied.

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Hypotensive effects of clonidine and chlorthalidone

Controlled clinical trial of drugs administered singly and in combination

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Substantial lowering of blood pressure by drugs in hypertensive patients is often associated with untoward effects. Thus the search continues for consistently effective blood pressure lowering agents devoid of significant side effects Clinical observations[1] have suggested that the new hypotensive drug clonidine lowers the blood pressure when taken in both the supine and standing positions without producing significant orthostatic hypotension [2,3] Since no carefully controlled double blind clinical trials of this drug have been reported to date the following study was designed to compare the hypotensive effects of clonidine and chlorthalidone administered singly and in combination in patients who had been receiving a placebo for one month before the double blind evaluation

Methods

Thirty patients of both sexes were studied as outpatients at the University Hospitals Each patient in the study had been followed in the Hypertensive Clinic for several months or years and therefore knew the investigators and was familiar with the environment of the clinic Written informed consent was obtained from each patient Inclusion in the study required that the patient s diastolic blood pressure averaged 95 mm Hg or greater during the last two weeks of a one month placebo control period During this placebo period each patient was seen and examined on three visits at intervals of two weeks. Systolic and diastolic arterial pressures and heart rates were recorded in the supine and standing positions immediately and 5 minutes after assuming these positions. No patient received antihypertensive medication for at least two weeks before the trial period Only cooperative nondiabetic patients without malignant or curable hypertension or other serious and incapacitating illnesses were studied All patients had a complete history and physical examination Laboratory tests included a hemoglobin hematocrit white blood cell count sedimentation rate urinalysis chest x ray electrocardiogram intravenous pyelogram and serum levels of creatinine uric acid

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bilirubin sodium potassium alkaline phosphatase glutamic oxaloacetic transaminase, serum proteins, two-hour postprandial blood sugars, cholesterol and direct and indirect Coombs tests. In addition aortograms and appropriate tests for pheochromocytoma and other rare forms of hypertension were performed when indicated. Those patients accepted into the study were assigned in a random double blind fashion by a statistician into three groups. Ten patients received clonidine and a chlorthalidone placebo ten patients received chlorthalidone and a clonidine placebo and ten patients received chlorthalidone and clonidine All medications were given orally Medications were dispensed by a pharmacist not connected with this study in accordance with the randomization procedure. The placebo tablets were indistinguishable from tablets with active contents. Chlorthalidone, 50 mg per day or its placebo was taken by each of the 30 patients throughout the study The initial dose of clonidine material was 300 mcg per day or the equivalent dosage of its placebo in four divided doses. At subsequent visits at intervals of two weeks the physician added 75 mcg of clonidine every 8 hours (or its placebo) if the diastolic blood pressure was 95 mm Hg or greater The upper dosage limit of 1,200 mcg., set before the trial, had to be reached by the third month of the study so that there would be no change in dosage during the last month of the study If a patient developed significant orthostatic hypotension or other untoward side effects, the dosage of clonidine or its placebo was reduced to a lower level and maintained at that level for the remainder of the study

During subsequent visits the patients were questioned concerning symptoms and were examined for adverse effects. Blood pressures and heart rate were taken in the supine and standing positions both immediately and 5 minutes after the patient had assumed these positions. Cessation of sound was our criterion for diastolic blood pressure Retinal examination was performed by the authors and by an ophthalmologist. Weights were recorded at each visit Hemoglobin hematocrit, white blood cell count, sedimentation rate urinalysis, electrocardiogram and serum levels of alkaline phosphatase glutamic oxaloacetic transaminase, uric acid creatinine bilirubin sodium potassium and direct and indirect Coombs tests and a two-hour postprandial blood sugar were measured monthly

At the beginning of the study it was decided that only the values for blood pressure and heart rate obtained 5 minutes after the supine and standing positions were assumed would be *analyzed*. The average blood pressures and heart rates after each of the three treatments were compared to their respective control values obtained during the placebo period The changes in these variables produced by each of the three treatments also were compared to each other

The data were analyzed by analysis of variance. Within-group comparisons utilized a randomized complete-block design while between-group comparisons utilized a completely random design Comparison of appropriate individual means utilized orthogonal contrasts. Mean values are presented with the standard error A probability of 0.05 or less was used as the criterion for statistical significance.

One patient in the chlorthalidone-alone group failed to return after the seventh visit of the double-blind phase of the study (the 900 mcg level of clonidine placebo) All other patients completed the entire trial. Average blood pressures and heart rates recorded during the last two visits of the control period those obtained after the 300 mcg dose level of clonidine or its placebo (alone and in combination with chlorthalidone) and those recorded during the final two weeks of the study in all patients were included in the analyses. The maximum allowable daily dosage of clonidine was not reached during the final month of this study in some patients because of occasional instances of excessive sedation dizziness, or the attainment of satisfactory blood pressure reductions on smaller doses

Results

Patient characteristics Each treatment group consisted of 6 men and 4 women All were white. The average age of those patients receiving chlorthalidone alone was

*Table I Effect of treatment in 30 hypertensive patients**

Treatment	*Blood pressure (mm Hg)*				*Heart rate (beats per minute)*		*Weight (pounds)*
	Systolic		*Diastolic*				
	Supine	*Standing*	*Supine*	*Standing*	*Supine*	*Standing*	
Clonidine (10)†							
Control	168 ± 10	167 ± 9	109 ± 4	112 ± 4	76 ± 4	87 ± 5	172 ± 8
300 mcg	158 ± 11	152 ± 11	100 ± 6	101 ± 5	73 ± 4	84 ± 5	173 ± 8
Final dose	159 ± 13	150 ± 14	102 ± 7	99 ± 7	70 ± 4	72 ± 4	174 ± 9
Probability	NS	<0 05	NS	<0 05	NS	<0 05	NS
Chlorthalidone (10)†							
Control	173 ± 9	172 ± 8	104 ± 3	108 ± 3	84 ± 4	91 ± 3	165 ± 10
300 mcg	163 ± 7	159 ± 9	103 ± 5	103 ± 4	87 ± 5	95 ± 4	163 ± 10
Final dose	157 ± 9	153 ± 9	96 ± 4	101 ± 5	86 ± 4	95 ± 3	165 ± 11
Probability	NS	<0 01	NS	NS	NS	NS	NS
Clonidine and chlorthalidone (10)†							
Control	185 ± 8	180 ± 8	113 ± 3	113 ± 4	82 ± 4	89 ± 4	165 ± 14
300 mcg	159 ± 9	154 ± 8	99 ± 4	99 ± 4	79 ± 4	85 ± 4	163 ± 14
Final dose	151 ± 7	144 ± 8	96 ± 3	95 ± 3	82 ± 4	90 ± 5	164 ± 15
Probability	<0 01	<0 05	<0 01	<0 01	NS	NS	NS

*Control values represent the average of the last two eeks of the control period for each group. Treatment values are those recorded while the patient ere receiving 300 mcg of clonidine or it placebo and the verage of the values recorded at the highest final dose level during the final t eeks of the trial. Probability level is for the comparison of control with the averaged effect of clonidine at 300 mcg. and that at the final dosage. I no instance is the effect of the final dose significantly different from the effect at the 300 mcg. dose level.

†Indicates the number of patient in each group (10)

41 years while the ages of those patients receiving clonidine alone and in combination with chlorthalidone averaged 44 and 46 years respectively Analysis of the data at the end of the control period indicated that there were no significant differences between the groups in regard to supine or standing blood pressures heart rates or body weight Laboratory test values for the three groups during the control period also were similar

Effects of the three treatment regimens on blood pressure heart rate and body weight Table I summarizes these results

CLONIDINE ALONE GROUP The average daily dose of clonidine during the final month of study was 668 mcg with a range of 300 to 1 125 mcg Only the average systolic and diastolic pressures taken in the standing position after 300 mcg and after the final dose level of clonidine were significantly less than their respective placebo controls Five of the 10 patients had arterial blood pressures (taken in the standing position) of 140/90 mm Hg or less, at the end of the study Two patients had no reductions while the other 3 patients showed only minor reductions. On the other hand in the supine position the average systolic and diastolic arterial pressures after clonidine were not significantly lower than their respective placebo control values Heart rates taken with the patient standing were reduced from control values by clonidine in 8 of the 10 patients ($p < 0.05$) Heart rates taken with the patient in the supine position and body weights were not changed appreciably from control levels.

CHLORTHALIDONE ALONE GROUP The final daily average placebo dose was equivalent to 975 mcg of clonidine with a range of 150 to 1 200 mcg In the standing position systolic arterial pressures decreased in 9 of the 10 patients receiving chlorthalidone alone ($p < 0.01$) The average diastolic

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Table II. Comparison of the changes in blood pressure and heart rate recorded at the highest final dose of each treatment

	Clonidine (10)	*Chlorthalidone* (10)	*Clonidine and chlorthalidone* (10)	p†
Blood pressure—supine (mm. Hg)				
Systolic	−9 ± 5‡	−16 ± 5	−34 ± 8	<0 025
Diastolic	−7 ± 6	−8 ± 4	−17 ± 4	NS§
Blood pressure—standing				
Systolic	−17 ± 7	−19 ± 6	−38 ± 7	<0 025
Diastolic	−13 ± 6	−7 ± 5	−18 ± 4	NS
Heart rate (beats/minute)				p‖
Supine	−6 ± 3	+1 ± 3	+0 ± 3	NS
Standing	−10 ± 3	+4 ± 4	+1 ± 4	<0 01

*Number of patients in each treatment group.
†Indicates probability level for comparison of the combination with the average changes in blood pressure resulting from clonidine alone and chlorthalidone alone. In no instance is the effect of clonidine alone significantly different from that of chlorthalidone alone.
‡Minus sign indicates reduction and plus sign an increase.
§NS, not significant.
‖Indicates probability level for comparison of the effect of clonidine with the averaged changes in heart rate resulting from chlorthalidone alone and the combination. In no instance was the effect of chlorthalidone alone significantly different from the combination.

pressure in the standing position and systolic and diastolic blood pressures in the supine position the heart rate and body weight did not change appreciably ($p > 0.05$) during chlorthalidone therapy

CLONIDINE AND CHLORTHALIDONE GROUP The average daily dose of clonidine for these 10 patients during the final month of the study was 610 mcg with a range of 100 to 1,200 mcg In the supine position systolic and diastolic pressures were lowered appreciably after the 300 mcg. dose level of clonidine (plus chlorthalidone) in 9 of the 10 patients ($p < 0.01$) After the higher doses of clonidine the final average arterial pressure taken in the supine position was 152/96 mm Hg ($p < 0.01$) In the supine position 4 of the 10 patients had arterial pressures of 140/90 mm Hg or less. Systolic and diastolic arterial pressures taken with the patient standing also were reduced significantly after this combination of drugs in 9 of the 10 patients. At the end of the study 6 patients (while standing) had a systolic pressure of 140 mm Hg or less, and 7 of the 10 patients had a diastolic pressure less than 95 mm. Hg Heart rates taken with the patient in either position and body weights were not altered appreciably by this treatment.

Comparative effects of the three treatments A comparison of the changes in blood pressure and heart rates produced by the three treatment regimens at their highest dosage is summarized in Table II Patients receiving clonidine in combination with chlorthalidone had greater reductions in systolic pressures taken in supine and standing positions, than the patients who received either treatment alone ($p < 0.025$) Although the diastolic pressure reductions, in supine and standing positions, were *nearly double* the average of those obtained with either treatment alone, the probability that the observed differences between treatments occurred by chance is greater than 5 per cent.

The average reduction in heart rate, taken in the standing position, of 10 beats per minute produced by clonidine alone was greater than that resulting from chlorthalidone alone or in combination with clonidine ($p < 0.01$) In patients receiving clonidine alone heart rates taken in the supine position averaged 6 beats per minute lower than control values, while in patients receiving chlorthalidone alone and in combination with clonidine heart rates were not changed from placebo control levels. This apparent difference in the

effect of clonidine alone on heart rate when taken in supine position from the effects of the other two treatments was not significant at the 5 per cent level

Effects of the three treatments on laboratory tests The average values of hematocrit white blood cell and differential cell counts sedimentation rate serum levels of alkaline phosphatase glutamic oxaloacetic transaminase uric acid sodium and glucose obtained during any of the three treatments were within normal ranges and not significantly different from their respective control levels obtained before the start of the double blind trial

In the group receiving clonidine alone serum creatinine levels increased from 0 87 ± 0 09 to 1 0 ± 0 08 mg per cent a change of little clinical importance Clonidine did not alter serum potassium levels appreciably The average level at the end of the study was 4 3 ± 0 2 mEq per liter as compared to the placebo control level of 4 2 ± 0 2 mEq per liter ($p > 0.05$) One patient in this group had a weakly positive indirect Coombs test in the control period and after clonidine Another patient developed a weakly positive indirect Coombs test only after clonidine

The average serum potassium level in the group receiving chlorthalidone alone fell from 4 1 ± 0 2 mEq per liter in the control period to 3 5 ± 0 2 mEq per liter after treatment ($p < 0.05$) No patient in this group had a positive direct or indirect Coombs test after chlorthalidone

In the group receiving both drugs serum potassium levels were reduced from 4 2 ± 0 2 mEq per liter to 3 2 ± 0 1 mEq per liter ($p < 0.05$) Supplemental oral potassium chloride was given to those individuals with low serum levels One patient developed a weakly positive indirect Coombs test and 2 patients developed a weakly positive direct Coombs test after treatment.

Toxic effects of the three regimens All but 1 of the 30 patients who entered the four month double-blind trial completed the study In no instance was it necessary to discontinue drug therapy because of toxicity All but 8 patients had some symptoms that might have been related to drug therapy Among the 10 patients receiving clonidine alone 6 reported mild dizziness 1 had mild dryness of the mouth and 7 complained about sedation Two patients had no side effects after clonidine. Among the 10 patients receiving chlorthalidone alone 4 did not report any side effects, 3 patients had mild sedation 2 described mild dryness of the mouth and 1 patient reported mild dizziness. Among the 10 patients receiving the combination of clonidine and chlorthalidone 2 had no side effects 5 patients reported mild sedation, 4 complained about mild dizziness, and 4 patients had mild dryness of the mouth One patient who achieved nearly normal blood pressures while receiving the combination of 900 mcg of clonidine per day with chlorthalidone developed severe agitation nausea vomiting diarrhea, and hypertension within 12 hours following discontinuation of clonidine at the conclusion of the study Reinstitution of clonidine was associated with prompt relief of symptoms and a return of blood pressures to near normal levels A single instance of skin rash that healed spontaneously in two weeks also was reported by this patient during the second week of the study None of the above side effects persisted in any patient. Ophthalmologic examination at the end of the fourth month of the study revealed no changes from those observed during the control period

Toxic effects in a 19 month-old boy In June 1969 a 19 month-old boy D M consumed two 300 mcg tablets of clonidine by accident He and his parents were visiting the home of a patient who was a participant in this study Earlier that morning before the ingestion the patient had vomited several times. One-half hour following the ingestion of the tablets, he was noted by his parents to be pale and drowsy and because of this he was admitted to the Pediatrics Service at the University of Iowa Hospital On physical examination the patient was lethargic but easily arousable and quite irritable. He would not walk His skin was pale The heart rate was 100 beats per minute the respirations were 32 beats per minute and regular Blood pressure taken in the supine position with a 3 inch cuff was 80/40 mm Hg Examination of the cardiovascular pulmonary and neurologic sys

tens was otherwise normal. The complete blood count sedimentation rate blood sugar blood urea nitrogen and serum creatinine were within normal ranges. The patient was hospitalized for observation He was given maintenance fluids intravenously (1,500 c.c. per square meter per day) By the next morning he was alert not irritable and the blood pressure was stable at 100/60 mm Hg Intravenous fluids were discontinued and the patient was discharged

Comment

The precise mechanism by which clonidine lowers arterial pressure is not clear In animal studies the majority of evidence indicates that clonidine exerts its hypotensive effects by reducing central sympathetic outflow to the heart.[1-3] Scriabine and associates[4] have presented data suggesting that clonidine also induced a slowing of the heart by peripheral sympathetic blockade Consistent reductions in heart rate both in animals[4-7] and in man have been reported Total peripheral resistance was found to be decreased in human studies after clonidine therapy Onesti and coworkers reported decreased stroke volume following oral administration of clonidine while Muir Burton, and Lowrie[8] were unable to detect appreciable reductions in stroke volume after intravenous administration of clonidine in man In animals, both alpha adrenergic blockade with tolazoline[2] and beta-adrenergic receptor blockade [3] have been reported to abolish the hypotensive effects of clonidine

Our data indicate that clonidine alone only lowered systolic and diastolic blood pressures when taken in the standing position while the combination of clonidine and chlorthalidone consistently lowered systolic and diastolic blood pressures in both the supine and standing positions. Furthermore the combination lowered systolic pressures in both the supine and standing positions more than either of the drugs taken alone

Clonidine alone significantly lowered the heart rate taken in the standing position while no appreciable changes in the heart rate, also taken in the standing position occurred in patients taking the combination of chlorthalidone and clonidine. The explanation for the lack of reduction in heart rate in patients taking the combination of drugs is not clear A change in blood volume produced by the diuretic action of chlorthalidone is one possible explanation although body weight did not decrease in patients taking this combination

Although systolic and diastolic pressures taken in the standing position were decreased significantly in patients receiving clonidine alone pulse pressure did not change appreciably Since heart rate decreased this suggests that the effect of clonidine alone on blood pressure might have partially resulted from interruption of the central sympathetic outflow to the heart as suggested by Magus and Long In patients receiving the combination there were greater decreases in systolic than diastolic blood pressures. Since heart rate did not change significantly in these patients this suggests that the primary effect of this drug combination was on myocardial contractility arterial or venous resistance or both These observations would be in agreement with those of Onesti and associates.[1]

Our short term experience with clonidine indicates that there are relatively few side effects associated with its use. Side effects were not of sufficient magnitude to cause discontinuation of therapy in any of the patients. The most common symptoms were dryness of the mouth sedation and dizziness. In all patients, these symptoms subsided spontaneously The accidental ingestion of 600 mcg of clonidine in a 19 month-old child resulted in sedation and mild hypotension. These symptoms also subsided spontaneously within 24 hours without specific treatment Four patients taking clonidine alone or in combination developed weakly positive Coombs tests. This was not associated with a change in the hematocrit or bilirubin concentration or clinical evidence of hemolysis. The hyperglycemia observed in rats treated with high doses of clonidine by Rehbinder and Deckers[9] was not observed in our patients. Two-hour postprandial blood sugars were not elevated by treatment with chlorthalidone or clonidine alone or in combination.

l revious evidence indicates that clonidine may be a useful alternative to currently available hypotensive agents in the treatment of mild or moderate hypertension if it is given with a diuretic. The reductions in arterial pressure resulting from clonidine therapy alone or in combination with chlorthalidone are similar to the reductions in pressure reported in hypertensive patients receiving methyldopa alone or in combination with chlorthiazide[11] and after hydralazine and hydrochlorothiazide therapy [12]

Summary

Thirty patients participated in a carefully controlled double blind trial of the new hypotensive agent clonidine Following four weeks of placebo therapy patients were randomly allocated to one of three treatment groups clonidine alone clonidine and chlorthalidone or chlorthalidone alone The dose of clonidine was increased from 300 to 1 200 mcg per day as tolerated over a four month period While clonidine alone only lowered significantly systolic and diastolic blood pressures taken in the standing position the combination consistently reduced these pressures taken in both the supine and standing positions Systolic blood pressures taken in the supine and standing positions were lowered significantly more in patients taking the combination than in those taking either drug alone Heart rate taken with the patient standing was reduced only with clonidine alone Serious toxicity was not observed One infant accidentally ingested clonidine but recovered quickly

Supplies of clonidine chlorthalidone, and placebos were provided by Paul A. Kennedy Jr M D of Geigy Pharmaceuticals, Ardsley N Y

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Right and left ventricular performance in chronic obstructive lung disease

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Hypertrophy and functional abnormalities of the right ventricle resulting from long-standing pulmonary disease have been well documented,[1-4] but derangement of the left ventricular function in such patients in the absence of other disorders affecting the left ventricle has not been clearly established. Left ventricular hypertrophy has been reported at autopsy in as many as 25 per cent of patients with chronic bronchitis, and Rao and associates recently demonstrated the occurrence of left ventricular failure in a group of patients with established chronic obstructive lung disease in the absence of other recognized causes of left ventricular dysfunction. However Williams and his co-workers[8] demonstrated a normal response of the left ventricle to an increase in afterload in patients with chronic obstructive lung disease. In patients with left ventricular disease the hemodynamic parameters may be normal at rest but exercise will frequently unmask significant functional abnormalities.[9] The present study was carried out to evaluate left ventricular hemodynamics at rest and during exercise in patients with chronic obstructive lung disease.

Methods

Twenty patients with clinical and radiologic evidence of chronic obstructive lung disease were studied. None had valvular heart disease or clinical evidence of coronary artery disease. Four patients had intra-arterial pressures between 150 and 170 mm Hg systolic but none had diastolic pressure greater than 90 mm Hg at rest. Eleven patients had no cardiac complications secondary to their lung disease (Group A) while nine patients (Group B) had "cor pulmonale" as defined by Harvey and Ferrer, that is, cardiac enlargement or failure in association with a disease process known to attack primarily the lungs or some aspect of the art of breathing and in so doing to compromise right ventricular function.

Cardiac catheterization was performed with the patients in the fasting postabsorptive state. Under local anesthesia the right brachial artery and an accompanying vein were isolated. A Cournand No. 9 double lumen catheter was placed so that its tip lay in the pulmonary artery and the proximal lumen in the right ventricle. A Sones No. 8 catheter was passed through the right brachial artery to the left ven

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tricle and a Cournand No 18 needle was placed in the left brachial artery

Patients were allowed to rest for at least 10 minutes before recording the control pressures in the right ventricle pulmonary artery left ventricle and brachial artery Following this the resting cardiac output was measured in duplicate by the dye dilution technique using indocyanine green The patients then exercised in the supine position on a bicycle ergometer against a resistance determined during a trial period of exercise the day prior to study

Exercise was carried out for three to eight minutes and pressures were recorded continuously during this period The car diac output was measured during the final one or two minutes of exercise and with each cardiac output determination oxygen consumption was measured by collecting expired air in a Tissot spirometer and analyzing it for CO_2 and O_2 by the Micro-Scholander technique Blood samples were withdrawn from pulmonary and brachial arteries at the time of the cardiac output determination and analyzed for Po_2 Pco_2 pH* and saturation† All pressures were measured with Statham P23Db strain gauges from a zero reference 5 cm below the angle of Louis and were recorded on a photographic recorder.‡

Systolic and diastolic pressures were calculated by averaging pressures over at least two respiratory cycles and the mean arterial pressures were obtained by elec tronic integration The left ventricular stroke work index (LVSWI) in g m./m² was calculated by the formula

$$LVSWI = \frac{SI \times (BAm - LVEDP) \times 13.6}{1\,000}$$

where SI = stroke index in ml./m² BAm = brachial artery mean pressure in mm Hg and $LVEDP$ = left ventricular end-diastolic pressure in mm Hg The right ventricular stroke work index (RVSWI) in g m./m² was calculated by the formula

$$RVSWI = \frac{SI \times (PAm - RVEDP) \times 13.6}{1\,000}$$

*Instrumentation Laboratories, pH/gas analyzer Model 113.
†American Optical Company Hemoreflector
‡DR8—Electronics for Medicine.

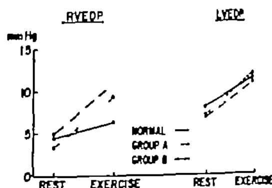


Fig 1 During exercise the right ventricular end-diastolic pressure (RVEDP) is abnormal in patients with chronic obstructive lung disease whereas the left ventricular end-diastolic pressure (LVEDP) remains within normal limits.

where SI = stroke index in ml./m² PAm = pulmonary artery mean pressure in mm Hg and $RVEDP$ = right ventricular end-diastolic pressure in mm Hg

A group of 14 patients studied by means of similar techniques and found to be free of cardiovascular disease were included as a normal group Selective coronary arteriograms were obtained in all normal patients and in three patients with chronic obstructive lung disease (Nos 11 19 and 20) and all readings were normal

Results

The results of pulmonary function tests on all patients are shown in Table I The hemodynamic and blood gas data for each patient along with mean values for the two groups and the normals are shown in Table II

Pressures (*Figs 1 and 2*) The mean value for right ventricular end-diastolic pressure at rest was 3 3 mm Hg in Group A and 4 8 mm Hg in Group B this value rose significantly in both groups during exercise to 9 5 and 11 1 mm Hg respectively The average left ventricular end-diastolic pressure at rest was 6 9 mm Hg in Group A and 7 0 mm Hg in Group B this pressure remained within normal limits in both groups during exercise being 12 2 and 11 2 mm Hg respectively The mean pulmonary artery pressure at rest averaged 17 2 mm Hg in Group A and 29 9 mm Hg in Group B ($P < 0.001$) It rose significantly in both groups ($P < 0.001$) with exercise averaging 35 9 and 52 1 mm Hg respectively Pulmonary artery mean pres-

Table I Results of pulmonary function tests in patients with chronic obstructive lung disease

Patient	Age	Vital capacity		FEV 1 sec./VC (%)	MVV		RV		TLC		RV/TLC (%)
		ML	% predicted		L./min.	% predicted	ML	% predicted	ML	% predicted	
Group A (without cor pulmonale)											
1. R. E.	45	3 200	67	34	33	40	2,950	403	6 375	108	85
2. W. P.	61	1 700	46	72	30	31	4 075	418	6 225	116	67
3. L. L.	57	2,300	65	24	31	30	3 125	571	6,335	123	54
4. J. M.	68	2 975	64	53	34	30	3 375	350	6 025	130	51
5. L. D.	47	3 050	75	25	36	30	3 875	403	7 100	134	55
6. H. A.	57	3 000	82	35	28	35	—	—	—	—	—
7. H. M.	64	3 475	94	43	41	41	—	—	—	—	—
8. W. D.	58	2,030	72	40	33	33	1 950	195	5 430	80	36
9. J. M.	63	4 850	144	41	65	69	2,000	201	6,500	130	21
10. E. T.	80	1 850	54	25	19	20	—	—	—	—	—
11. W. Y.	55	—	—	—	—	—	—	—	—	—	—
Group B (with cor pulmonale)											
12. C. T.	30	1 250	33	33	15	16	3 600	390	4 875	90	72
13. J. W.	41	3 000	82	58	71	70	3 000	415	4 025	125	49
14. J. K.	69	—	—	—	—	—	—	—	—	—	—
15. J. Q.	65	1 700	43	34	16	20	4 125	490	6 175	120	67
16. G. B.	66	2 300	63	24	19	23	2 650	272	5 000	94	53
17. J. P.	42	2,200	56	22	27	29	2 300	344	5 025	93	45
18. L. M.	56	925	23	48	15	21	—	—	—	—	—
19. L. W.	62	1,250	34	31	9	10	—	—	—	—	—
20. L. Mer.	45	2 250	58	62	33	30	1 125	130	3 600	73	31

Abbreviations: VC = vital capacity; FEV 1 sec/VC = timed vital capacity; MVV = maximum voluntary ventilation; RV = residual volume; TLC = total lung capacity.

sure in Group B was significantly higher than in Group A ($P < 0.02$) during exercise. The mean brachial artery pressure at rest was 99.6 mm. Hg in Group A and rose to 121.5 mm. Hg during exercise. In Group B these values were 91.2 and 110.8 mm. Hg respectively. The increase during exercise was similar in the two groups.

Cardiac output (Fig. 3). The resting cardiac index averaged 2.80 L./min./m.² in Group A and 3.48 L./min./m.² in Group B (NS). It rose during exercise to 4.77 and 4.83 L./min./m.², respectively, in the two groups. This represented a 70 per cent increase in Group A but only a 39 per cent increase in Group B and may be related to the lower oxygen consumption during exercise in Group B. The exercise factor* averaged 576 in Group A and 492 in Group B.

The resting stroke index was 33.7 ml./m.² in Group A and 37.7 ml./m.² in Group B. During exercise this increased to 42.8 ml./m.² in Group A ($P < 0.001$) and only 39.1 ml./m.² in Group B (NS), representing a change of 27 per cent and 4 per cent, respectively ($P < 0.005$).

Ventricular work. The right ventricular stroke work index at rest was 6.4 g.-m./m.² in Group A but 12.5 g.-m./m.² in Group B ($P < 0.001$). During exercise the stroke work index rose to 15.2 g.-m./m.² in Group A and 21.5 g.-m./m.² in Group B. The level during exercise was significantly higher in Group B than in Group A ($P < 0.05$).

Left ventricular stroke work index at rest was similar in the two groups, being 42.7 g.-m./m.² in Group A and 42.5 g.-m./m.² in Group B. During exercise this increased to 62.3 g.-m./m.² in Group A and to 52.4 g.-m./m.² in Group B. However, this value in Group A was not statistically different from that in Group B.

Blood gases. The average arterial oxygen

*Increase in cardiac output in ml. per 100 ml. increase in oxygen consumption.

Table II Hemodynamic and blood gas data at rest and during exercise in all patients

Patient	Heart rate (beats/min.)		PAm (mm Hg)		BAm (mm Hg)		RVEDP (mm Hg)		LVEDP (mm. Hg)		CI (L./min./m.		SI (ml/m²	
	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex
Group A (without cor pulmonale) n = 11														
1	94	140	18	40	93	133	0	6	3	6	3.33	6.14	35	[illegible]
[illegible]	79	99	14	30	90	88	3	10	8	15	3.52	5.39	44	[illegible]
3.	100	123	19	33	110	133	4	9	10	13	2.31	3.58	23	[illegible]
4.	87	110	[illegible]	48	11	[illegible]	5	13	10	12	3.63	3.11	43	[illegible]
5.	83	123	20	41	93	128	4	1	5	15	[illegible]	3.87	28	[illegible]
6.	73	97	13	[illegible]	93	109	3	7	7	11	3.17	4.76	45	[illegible]
7	72	91	18	39	114	140	4	13	8	20	3.61	[illegible]	30	[illegible]
8.	86	120	17	34	[illegible]	107	2	8	8	10	[illegible]	4.33	[illegible]	[illegible]
9	86	122	12	28	110	130	3	7	5	8	[illegible]	4.15	[illegible]	[illegible]
10.	75	118	17	42	90	120	2	10	7	15	[illegible]	4.53	27	[illegible]
11	66	108	[illegible]	35	90	118	6	9	5	9	2.33	[illegible]	27	[illegible]
Mean	83 7	114.0	17.[illegible]	35.9	99.6	[illegible]	3.3	9.5	6.9	[illegible]	[illegible]	4.77	33.7	[illegible]
± S.E.M	±2.6	±[illegible]	±0.9	±[illegible]	±3.0	±4.5	±0.5	±0.7	±0.7	±1.2	±0.19	±0.28	±[illegible]	[illegible]
Group B (with cor pulmonale) n = 9														
[illegible]	90	120	41	55	118	162		17	7	13	2.00	2.90	[illegible]	[illegible]
13.	90	111	23	39	73	87		5	3	5	3.23	5.43	[illegible]	[illegible]
14	117	138	40	50	78	90	7	10	10	14	4.98	5.46	42	[illegible]
15.	78	136	23	38	80	100	3	10	8	10	2.20	3.81	31	[illegible]
16.	90	102	[illegible]	39	92	83	3	7	7	8	2.09	3.14	[illegible]	[illegible]
17	78	132	25	62	77	110	3	10	7	16	3.06	4.27	[illegible]	[illegible]
18.	135	156	22	28	110	120	2	0	3	5	4.01	5.33	[illegible]	[illegible]
19	[illegible]	120	[illegible]	63	110	130	9	1	7	11	4.58	6.50	[illegible]	[illegible]
20.	72	110	31	65	85	115	12	20	13	16	4 41	6.51	61	[illegible]
Mean	93.9	125.0	29.9	[illegible]	[illegible]	110.8	4.8	11 1	7.0	11.[illegible]	3.45	4 83	37.7	[illegible]
± S.E.M.	±7.0	±5.7	±[illegible]	±6.0	±5.7	±8.3	±1.[illegible]	±[illegible]	±1.[illegible]	±1.3	±0.35	±0.46	±4.0	±[illegible]
Normals n = 14														
Mean	73.5	119 4	[illegible]	22.2	90.9	108.0	4.5	6.3	8.4	11.6	3.17	6.12	43.7	[illegible]
± S.E.M	±2.8	±4 4	±0.7	±1 4	±[illegible]	±3.1	±0.4	±0.9	±0.5	±1 4	±0.10	±0.33	±2.0	±[illegible]

Abbreviations: PAm = pulmonary artery mean pressure; BAm = brachial artery mean pressure; RVEDP = right ventricular end-diastolic ... index; LVSWI = left ventricular stroke work index; VO_2 = oxygen consumption; P_{O_2} = partial pressure of oxygen; O_2 Sat. = oxygen saturation ...

saturation at rest was 94.4 per cent in Group A and 89.6 per cent in Group B ($P < 0.005$). During exercise there was no change in Group A but the oxygen saturation fell significantly in Group B to 86.8 per cent ($P < 0.05$). The P_{O_2} at rest averaged 81.9 mm. Hg in Group A and 63.6 mm. Hg in Group B ($P < 0.01$). There was no significant change with exercise in either group but the P_{O_2} value during exercise in Group B was significantly lower than in Group A ($P < 0.005$). The P_{CO_2} at rest averaged 40.1 mm. Hg in Group A, rising to 46.8 mm. Hg during exercise ($P < 0.005$). In Group B it averaged 44 mm. Hg at rest and increased to 51 mm. Hg during exercise ($P < 0.01$). However, the differences between the two groups at rest and during exercise were not statistically significant.

Discussion

The pulmonary artery mean pressure (PAm) at rest in the patients without cor pulmonale, although within the accepted limits of normal, was higher than in our normal group. During exercise this group developed moderate pulmonary hypertension and abnormal right ventricular filling pressures. Although the increase in heart rate and stroke index during exercise

RVSWI g-m./m. R	RVSWI g-m./m. Ex	LVSWI g-m./m. R	LVSWI g-m./m. Ex	$\dot{V}O_2$ (ml./m.²) R	$\dot{V}O_2$ (ml./m.²) Ex	Exercise factor	P_{O_2} (mm. Hg) R	P_{O_2} (mm. Hg) Ex	O_2 Sat. (Vol. %) R	O_2 Sat. (Vol. %) Ex	P_{CO_2} (mm. Hg) R	P_{CO_2} (mm. Hg) Ex	pH R	pH Ex
8.7	22.6	43.3	63.9	149.3	595	646	88	88	90	89	45	60	7.30	7.25
6.8	14.8	40.5	54.0	158	628.5	329	86	96	94	98	30	40	7.29	7.37
4.7	9.5	31.4	47.5	130.5	438	444	82	88	95	98	40	39	7.40	7.33
8.5	22.1	58.6	70.7	131.8	436.8	441	88	89	92	92	49	63	7.28	7.33
6.1	13.2	34.5	46.6	139.9	530.7	398	74	74	94	94	39	55	7.45	7.35
8.9	11.3	49.9	66.2	124.3	408	634	100	103	95	109	42	47	7.45	7.37
9.5	21.1	72.1	97.2	161.7	453.8	620	118	90	98	96	39	47	7.40	7.35
6.8	12.7	35.3	47.6	230.8	453.8	343	88	88	92	88	38	39	7.41	7.37
3.9	8.8	33.7	58.3	147.8	490	602	80	85	95	99	25	32	7.45	7.41
5.8	18.0	30.7	82.4	112.3	540.4	609	82	78	98	95	46	54	7.35	7.31
8.0	12.9	31.7	54.3	—	—	—	78	72	84	93	38	38	7.37	7.38
6.4 ±0.8	14.2 ±1.5	42.7 ±4.0	62.3 ±4.9	150.4 ±10.2	496.2 ±18.5	670.0 ±42.0	81.9 ±4.6	79.9 ±4.1	94.4 ±0.7	94.4 ±1.1	40.1 ±1.7	48.5 ±2.6	7.41 ±0.01	7.36 ±0.01
12.1	21.9	32.0	48.0	128	294	305	47	60	86	85	54	61	7.27	7.28
9.8	22.8	34.8	54.1	160	608	553	64	60	85	84	46	61	7.34	7.32
10.0	21.5	38.6	40.9	187.3	328	349	—	—	—	—	—	—	—	—
8.3	10.7	33.3	34.3	113	331.3	645	78	78	93	92	42	56	7.43	7.27
9.7	13.6	34.5	31.6	117.4	276.4	281	68	58	92	85	38	38	7.41	7.27
11.7	23.8	37.2	41.2	149.4	411	463	58	40	88	79	44	53	7.41	7.26
7.8	12.8	42.6	61.6	164.8	452.4	480	64	88	88	88	35	39	7.42	7.25
15.6	31.6	70.0	89.4	—	—	—	77	67	93	90	46	51	7.38	7.23
13.3	36.3	68.9	70.7	164	433	680	87	53	91	89	45	47	7.35	7.31
12.3 ±1.4	21.6 ±2.5	42.8 ±4.4	52.4 ±6.6	140.7 ±10.4	399 ±40.3	492 ±45.3	63.6 ±3.2	60.1 ±3.7	88.8 ±1.1	88.8 ±1.4	44.0 ±2.1	51.0 ±2.8	7.39 ±0.01	7.34 ±0.01
4.0 ±0.3	11.3 ±0.9	40.1 ±2.6	68.8 ±3.5	141.0 ±3.8	981.6 ±21.6	687.0 ±37.5	—	—	—	—	—	—	—	—

pressure; LVEDP = left ventricular end-diastolic pressure; CI = cardiac index; SI = stroke index; RVSWI = right ventricular stroke work tion; P_{CO_2} = partial pressure of carbon dioxide; R = rest; Ex = exercise; S.E.M. = standard error of the mean.

was similar to that experienced by the normal patients (Fig 3) the right ventricular stroke work index was higher (Fig 4) and this is related to the increase in pressure work. In relating right ventricular stroke work index to right ventricular end-diastolic pressure it appears that these patients operate on an extension of the normal right ventricular function curve in keeping with the Starling mechanism. In the absence of signs of right ventricular hypertrophy the changes in filling pressure probably reflect directional changes in right ventricular volume rather than altered compliance.

The patients with cor pulmonale exhibited moderate pulmonary hypertension at rest which became severe during exercise associated with abnormal right ventricular filling pressures. In contrast to those without cor pulmonale these patients showed no significant change in stroke index during exercise although the heart rate response was similar. The right ventricular stroke work index was considerably higher due entirely to the increase in pressure work. This was accompanied by a further increase in right ventricular filling pressures. These increases may be due in part to decreased ventricular compliance. It seems, however

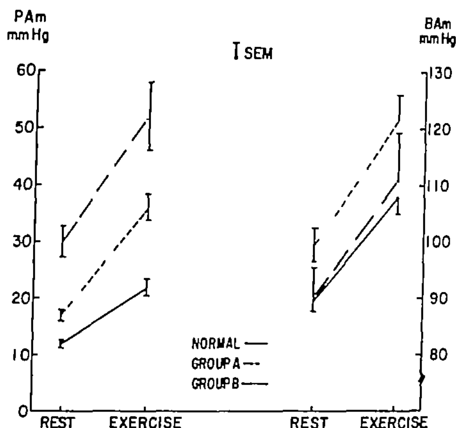


Fig 2 Pulmonary artery mean pressure (*PAm*) i higher than in normal patients at rest in those patients with and without cor pulmonale during exercise severe pulmonary hypertension develops. The brachial artery mean pressure (*BAm*) is normal at rest in patients with chronic obstructive lung disease and increases similarly during exercise in the three groups. *SEM* = standard error of the mean.

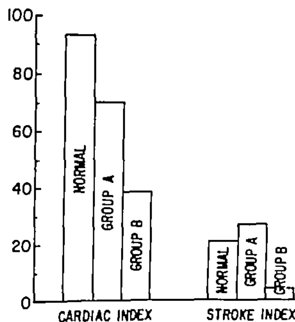


Fig 3 The percentile rise in cardiac index in response to exercise is lowest in the cor pulmonale group, and intermediate in patie ts without cor pulmonale The increase in stroke index in Group A is similar to that experienced by normal patients but is sig nificantly lower in Group B.

that patients with chronic obstructive lung disease and normal subjects describe a single right ventricular function curve with their individual positions on this curve determined by the pulmonary ar terial pressure

Since the rise in heart rate was similar in each group right ventricular function can be assessed by relating stroke index to right ventricular filling pressure (Fig 4) Both groups with obstructive lung disease behave quite differently from the normal subjects. The normal patients show a sig nificant increase in stroke output with little change in filling pressure while patients with cor pulmonale show little change in stroke output but a greater in crease in right ventricular end-diastolic pressure. The patients without cor pul monale show an intermediate response

It is well documented that in patients with left ventricular disease the filling pres sure may be normal at rest but frequently becomes abnormal during exercise [18, 21] Left

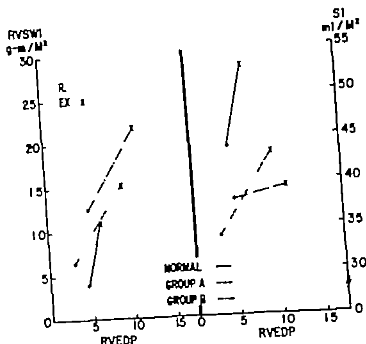


Fig. 4 Right ventricular stroke work index (*RVSWI*) is highest in patients with cor pulmonale both at rest (*R*) and during exercise (*Ex*). All three groups form a single right ventricular function curve, but patients with chronic obstructive lung disease operate on an extension of this curve with abnormal right ventricular end-diastolic pressures (*RVEDP*) during exercise. However when stroke index (*SI*) is related to the *RVEDP* patients with cor pulmonale show depressed right ventricular function.

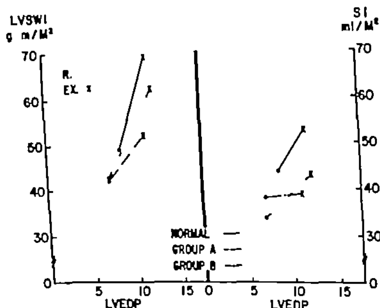


Fig. 5 Apparent depression of left ventricular function secondary to right ventricular dysfunction. This is due to diminished inflow into the left ventricle because of the reduced right ventricular stroke output secondary to pulmonary hypertension. *LVEDP* = left ventricular end-diastolic pressure; *LVSWI* = left ventricular stroke work index.

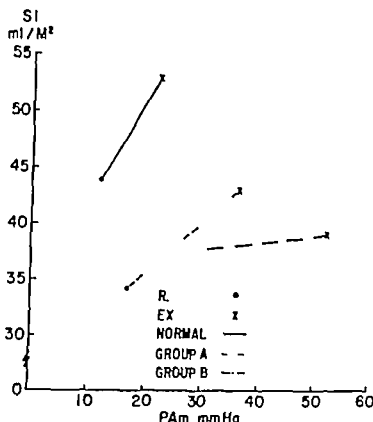


Fig. 6. Stroke output in patients with chronic obstructive lung disease is significantly compromised secondary to the increased pressure work. *PAm* = pulmonary artery mean pressure. *R* = mean values at rest, *Ex* = mean values during exercise, and *SI* = stroke index.

ventricular end-diastolic pressure in our patients with obstructive lung disease was normal during exercise and thus it is unlikely that left ventricular function was depressed. This is in keeping with the observations of Williams and his co-workers[8] who found a normal response of the left ventricle to an increase in afterload in patients with obstructive lung disease.

When one considers the changes in either stroke index or in left ventricular stroke work index in relation to changes in filling pressures, it appears that patients with chronic obstructive lung disease had depression of the left ventricular function (Fig. 5). We believe that this apparent depression of the left ventricular function may be related to a decreased right ventricular stroke output due to pulmonary hypertension during exercise, thus reducing the left ventricular inflow (Fig. 6). An analogous situation of spurious depression of one ventricle when the function of the other is compromised may be found in experimental studies. Case and co-workers[13] have shown that depression of the right ventricular function can be seen in dogs when the right atrial pressure is related to the right ventricular stroke output with a depressed left ventricular function secondary to a reduced left coronary flow. However, when right ventricular stroke work was related to right atrial pressure in those studies, the right ventricular function was normal.

One might argue that if the left ventricular inflow is diminished, the filling pressure should be lower than observed here in keeping with the Starling relationship. The rise in the left ventricular filling pressure in patients without cor pulmonale following exercise is similar to that seen in the normal subjects and is probably related to the increased volume load as these patients increased their stroke output. The left ventricular filling pressure observed during exercise may also be spuriously elevated in patients with chronic obstructive lung disease due to the increase in intrathoracic pressure associated with exercise.

It is concluded that in patients with chronic obstructive lun[illegible]sease the ventricular function i[illegible] res to exercise and the ri[illegible]

work is compromised because of the increased pressure work.

Summary

Hemodynamic studies at rest and during exercise were carried out in 20 patients with chronic obstructive lung disease, nine of whom had cor pulmonale. The right ventricular end-diastolic pressure which was normal at rest reached abnormal levels during exercise whereas the left ventricular end-diastolic pressure remained within normal limits. The stroke index rose during exercise by 27 per cent in patients without cor pulmonale, but rose only 4 per cent in patients with cor pulmonale ($P < 0.005$). Relating right ventricular end-diastolic pressure to stroke index, right ventricular function appeared depressed but when right ventricular stroke work index was considered, it appeared that right ventricular function was normal. This apparent paradox is probably due to the increase in pressure work accomplished at the expense of output work. Left ventricular end-diastolic pressure remained within normal limits during exercise in these patients. However the left ventricular function curves obtained in the conventional manner appear depressed. This may be secondary to compromised stroke output of the right ventricle and hence may indicate a diminished inflow to the left heart.

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An evaluation of contourography as a technique for electrocardiographic data compression

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The contourogram is a display which can be utilized to study large volumes of electrocardiographic (ECG) data in a compact form. Changes in cardiac rate, rhythm, and wave form can be identified by contourography. We have applied the method to the study of ECG data from patients with acute myocardial ischemia. This report summarizes the usefulness, advantages, and limitations of the method for analyzing these data.

Materials and methods

Contourograms were prepared for more than 700 hours of ECG data obtained from 25 patients admitted to the Myocardial Infarction Research Unit. All patients had had or were suspected of having an acute myocardial infarction. A five lead ECG cable utilizing Mennen Greatbach silver-silver chloride pellet electrodes was attached to the anterior chest with adhesive tape using Hewlett Packard Sanborn Redux Creme as the conductive interface. Three ECG signals corresponding to Leads I, II, and V_1 were simultaneously transmitted to a Hewlett Packard 1520A Vectorcardiograph amplifier. The signals were then distributed to a Honeywell 7600 FM 1/2 inch tape recorder running at 1⅞ inches per second. The electrocardiogram (ECG) was also continuously monitored on an oscilloscope. Contourograms were reviewed, and areas for further study were identified and compared to standard paper write-out.

The details of the instrumentation as developed by one of us (G. N. W.) have been described.[1-3] A brief resume of the pertinent aspects of the technique will be given. The key features in contourography involve utilization of the three-dimensional

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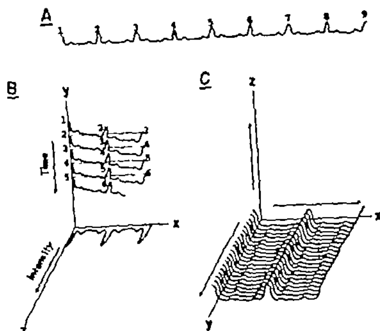


Fig. 1. The construction of contourograph. *A*, Standard ECG with each complex numbered. *B*, The superimposition of the ECG complexes is shown. Note that Complex *2* is the second complex in the first line and that part of this same Complex *2* starts the second line. Intensity is shown on the *Z* axis. Positive deflections are shown with increased intensity. *C*, A completed contourograph is shown.

aspect of the cathode ray tube vertical signal deflection flexible time base and intensity modulation. Fig. 1 illustrates the method in a diagrammatic fashion.

Contourographs for this study were made using a Tektronix 561A oscilloscope, with two type 260 plug-ins and a Beattie-Coleman 70 mm camera with a continuous motion film magazine. A control unit on the oscilloscope generates a linear horizontal sweep which is triggered by the ECG R wave. A refractory period of 150 msec. (relative to real data time) is built into the circuitry to prevent the sweep from being retriggered by a succeeding T wave. The sweep continues across the scope face until the second R wave appears or for a period of four seconds, whichever is shorter. Thus the sweep length is controlled by R R intervals. The sweep is usually adjusted so that two normal cardiac cycles fall within the width of the oscilloscope screen.

Adjustment of the cathode ray tube beam allows inscription of positive ECG deflections, while negative ECG deflections appear blank. The intensity of the beam is made proportional to the amplitude of the ECG signal; thus, the taller an R wave the brighter its image. The control unit adjusts amplitude and offset to match cathode ray tube phosphor and film characteristics to provide optimum gray scale variation on the film.

The ECG is played back into the contourographic apparatus at 64 times real time (120 inches per second) and is photographed on continuously moving 70 mm.

Table I. Arrhythmias detected with contourography

Sinus arrhythmia
Sinus tachycardia
Ventricular premature contractions
Accelerated idioventricular rhythm
First degree atrioventricular block
Atrial premature contractions
Atrial fibrillation
Atrial flutter
Paroxysmal atrial tachycardia
Nodal tachycardia
Ventricular tachycardia
Second degree atrioventricular block
Atrial bigeminy

An evaluation of contourography as a technique for electrocardiographic data compression

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*George N Webb M S ***
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The contourogram is a display which can be utilized to study large volumes of electrocardiographic (ECG) data in a compact form Changes in cardiac rate rhythm and wave form can be identified by contourography We have applied the method to the study of ECG data from patients with acute myocardial ischemia This report summarizes the usefulness advantages, and limitations of the method for analyzing these data

Materials and methods

Contourograms were prepared for more than 700 hours of ECG data obtained from 25 patients admitted to the Myocardial Infarction Research Unit All patients had had or were suspected of having an acute myocardial infarction A five lead ECG cable utilizing Mennen-Greatbach silver-silver chloride pellet electrodes was attached to the anterior chest with adhesive tape using Hewlett Packard Sanborn Redux Creme as the conductive interface. Three ECG signals corresponding to Leads I II and V_2 were simultaneously transmitted to a Hewlett Packard 1520A Vectorcardiograph amplifier The signals were then distributed to a Honeywell 7600 FM ½ inch tape recorder running at 1⅞ inches per second The electrocardiogram (ECG) was also continuously monitored on an oscilloscope Contourograms were reviewed and areas for further study were identified and compared to standard paper write-out

The details of the instrumentation as developed by one of us (G N W) have been described[1-3] A brief resume of the pertinent aspects of the technique will be given The key features in contourography involve utilization of the three-dimensional

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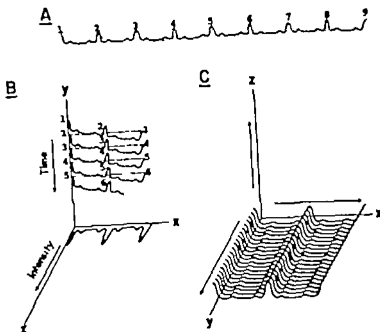


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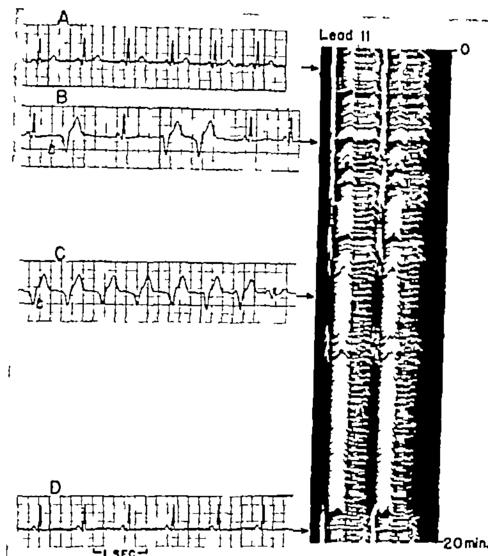


Fig. 2 Normal sinus rhythm interrupted by accelerated idioventricular rhythm. Twenty minutes of continuously recorded Lead II ECG. The first few minutes are normal sinus rhythm with a regular rate of 75 per minute (illustrated at point A). At point B sinus rhythm is interrupted by short runs of accelerated ventricular rhythm at a rate slightly faster than the sinus mechanism. These two rhythms alternate until point C when the idioventricular mechanism becomes dominant. The QRS complex is wide. Its deflection negative (hence not inscribed on the contourogram) and the ST segments are elevated and slope upward to a taller T wave than that with sinus rhythm (hence its greater intensity). During idioventricular rhythm, P waves occur infrequently and are not usually followed by normally conducted beats due to the more rapid rate of the aberrant rhythm. When sinus rhythm returns at point D T waves have become flat (confirmed by the ECG tracing shown to the left)

film Film movement through the camera can be varied from 1/16 inch to 8 inches per second At the slowest rate 3 5 inches of film are exposed for each hour of ECG data at the fastest film rate 3 75 feet of film would be needed for one hour of ECG data All contourographs shown in the illustrations were processed so that one hour of real time ECG data required 28 inches of film

In the study reported here 24 hours of ECG data required approximately one and one half hours of technician time for processing the tape and the development of the film Ordinarily tapes were changed every 12 hours and the information then processed and photographed

Results

Of the 700 hours of taped ECG processed 525 hours provided contourograms of interpretable quality I e because of the artifact 25 per cent of the time the contourograms contained insufficient informa

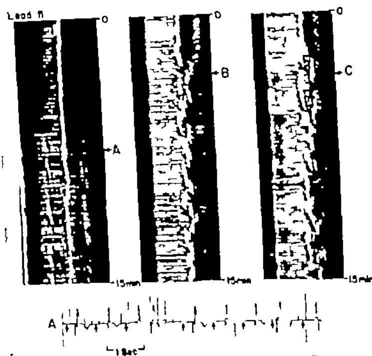


Fig. 3. Sinus rhythm with first degree atrioventricular block and premature ventricular contractions. The prolonged P R interval and low amplitude bifid P waves (indicated by arrows) are shown on the ECG tracing at the bottom. (Spike artifacts on the standard ECG tracing are due to playback artifact from the tape.) In the panel on the left, the Q wave is represented by a dark band on the contourogram which is followed by an upright R wave and an ST segment sloping down to an inverted T wave. The rate is regular until point *A* when numerous upright and widened RS deflections occur; these are premature ventricular contractions (shown in the ECG at the bottom). At point *B* sinus arrhythmia appears. At point *C*, sinus irregularity persists, and there is a marked change in T wave morphology; previously inverted T waves have now become upright while the ST segment are slightly depressed.

tion on which to make a clinical judgment. Inadequate ECG signal was responsible for 80 per cent of the unreadable records, while processing difficulties (failure of triggering, improper film exposure, failure to center oscilloscopic image on the screen, etc.) accounted for the remaining 20 per cent.

Normal sinus rhythm constituted the vast majority of observed rhythms. The type of arrhythmias demonstrated by the contourographic technique are shown in Table I in order of the frequency of their occurrence. Although minor changes in QRS wave form were difficult to detect, major changes in QRS configuration were readily identified. ST segment elevation or depression was frequently observed but the magnitude of change could not be quantitated. Changes in T wave contour were readily identified. Changes in P wave morphology were subtle and less easily identified.

Figs. 2 to 8 have been selected to illustrate the types of ECG information which can be obtained with the use of this technique.

Processing modifications were studied in an effort to enhance the sensitivity of the method. The rate of film movement

*It should be emphasized that no special effort was made to secure high quality ECG tracings during the period these data were being collected. Recently we have conducted a study, utilizing the same electrode placement, to learn how the ECG artifacts might be reduced. Technicians and nurses were carefully instructed in meticulous attention to skin preparation, electrode placement, and immediate attention to the artifacts when they were seen on the monitoring oscilloscope. Artifacts were reviewed and discussed. By these measures, the frequency of technically unacceptable signals is less than 5 per cent of monitoring time (instead of 30 per cent of monitoring time as was found during the period of study reported).

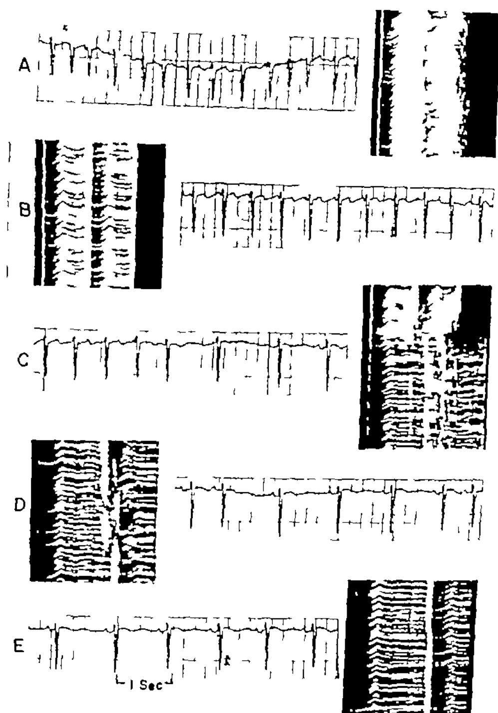


Fig 4 Atrial fibrillation and flutter reverting to sinus rhythm. Each contourogram represents 5 to 7 minutes of contourographic data selected from a contin ous strip obtained over a five-hour period. The contourogram was made from Lead II while the standard tracings shown are from a simultaneously obtained precordial lead. The totally uneven pattern of upright R waves in the contourogram at *A* represents atrial fibrillat on at a rapid rate. After Digoxin had been given intravenously fibrillation is replaced by atrial flutter with a 2 1 atrioventricular response, as shown in *B* In *C*, flutter is replaced by a slower more irregular rhythm with upright P R, and T waves. In *D* this is more clearly seen to be sinus rhythm with frequent premature atrial contractions. In panel *E*, regular sinus rhythm appears.

through the camera was varied to determine an optimal rate which would preserve single ectopic sensitivity while still providing adequate data compression The rate selected was 28 inches of film per hour of real time ECG information Modifications in the signal display also were studied to assess their sensitivity in detecting premature ventricular contractions. Fig 7 illustrates a comparison between scalar lead

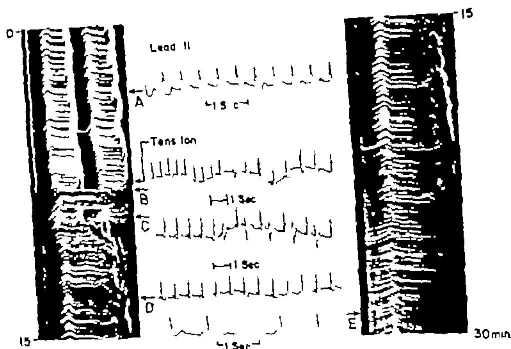


Fig. 3. Rapid supraventricular tachycardia reverting to sinus rhythm. The left panel shows upright R waves, depressed ST segments, with biphasic terminally positive T waves, and absent P waves. This rhythm is supraventricular tachycardia at a rate of 136. At point *B* 5 mg. of Tensilon was given intravenously and the tachycardia terminated. (Note that ECG tracings *B*, *C*, and *D* are recorded at 10 mm. per second.) At point *C*, irregularity persists, the mechanism of which cannot be identified on the contourogram but represents frequent aberrantly conducted beats (tracing *C*). Base-line shift and 60 cycle artifact also contribute to the difficulties in interpretation of this segment of the contourogram. The sinus mechanism becomes regular at point *D* and remains so thereafter. The ST segments are dark when compared to the T P segments at the time the tachycardia is present, indicating ST segment depression in panel *A*. As the rate slows, the ST segments become "lighter" and the ECG tracing confirms their return to the isoelectric base-line in panel *E*.

and vector loop contourograms from a patient with multifocal ectopic ventricular contractions.

Discussion

An ideal system for reviewing the large volumes of ECG data collected in acute coronary care areas would include the following features: (1) It would detect and quantitate changes in cardiac rate, rhythm, and wave form. (2) It would be completely sensitive to changes in ECG while rejecting artifactual variation in the signal. (3) It would provide alarm devices for ECG changes occurring outside preset limits. (4) It would provide analogue and digital information "on-line." (5) It would be able to retrieve past information for comparison. (6) It would provide a permanent record of compact analogue data. (7) It would perform all these functions with minimal and simple human intervention.

Available arrhythmia detection devices provide quantitative information about rate and ectopic rhythms; however, except for changes in QRS duration they do not detect alterations in wave form. The R-R interval histogram permits precise quantitation of heart rate but does not detect changes in wave form.[4-6]

Another system provides rapid review of 8 hour segments of ECG data for changes in rate, rhythm, and conduction.[4-6] The limitations of such instrumentation, particularly in the evaluation of ST segment and T wave alterations, have been recently reviewed. Modifications of this system with the addition of photographic representation of wave form changes, have substantially improved the analysis possible.[-u] Although the application of digital computer techniques to ECG monitoring

*Hewlett-Packard 7822A.

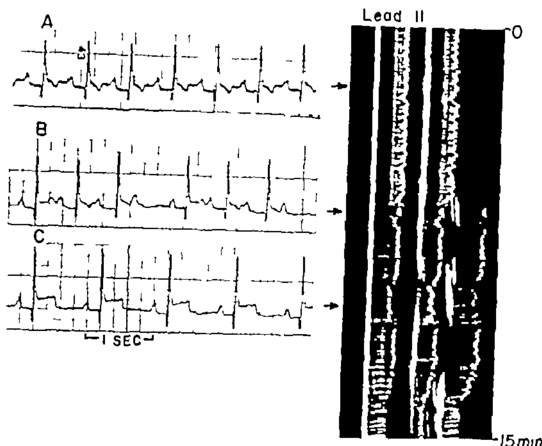


Fig. 6. Varying atrioventricular block with inferior infarction. At point *A* stable first degree heart block is present. As the atrial rate increases from 92 to 111 per minute at point *B* second degree atrioventricular block with 4:3 Wenckebach periods appear. The sinus rate increases to 120 at point *C* and 2:1 atrioventricular block appears.

analysis is of demonstrated usefulness, it is not widely available, it is expensive, and it does not preserve the analogue nature of the signal.[11, 13]

The contourogram has several advantages over techniques outlined above. It does not require a computer with its hardware and software complexities. As Figs. 2 to 7 illustrate, the ECG wave form remains unaltered, a desirable feature when analyzing the records. A permanent record of the analogue signal in this much reduced form can be stored and the tape erased. This study demonstrated that contourography has usefulness for ECG analysis in four areas. These are briefly discussed in the subsequent paragraphs and illustrated in Figs. 3 to 8.

The contourographic technique is most useful in *demonstrating abrupt or phasic changes in cardiac rate and rhythm which occur on a steady state background*. Fig. 2 illustrates this point and demonstrates an accelerated idioventricular rhythm which intermittently interrupts the patient's normal sinus mechanism. The abrupt conversion of a rapid supraventricular tachycardia following Tensilon is illustrated in Fig. 5. The effects of digitalization on atrial fibrillation, resulting in atrial flutter and finally in sinus rhythm, are demonstrated in Fig. 4.

Changes in wave form can generally be appreciated on the contourogram. Fig. 3 illustrates the reversion of inverted T waves to upright position, while Fig. 5 demonstrates changes in ST segment depression.

Trend information is nearly always discernible from the contourogram. The number of premature ventricular contractions per unit of time can be closely approximated as seen in Figs. 3 and 8. The effects of drugs on rate and rhythm may be demonstrated as shown in Figs. 4 and 5.

Contourography also *identified areas where more detailed analysis may be indi*

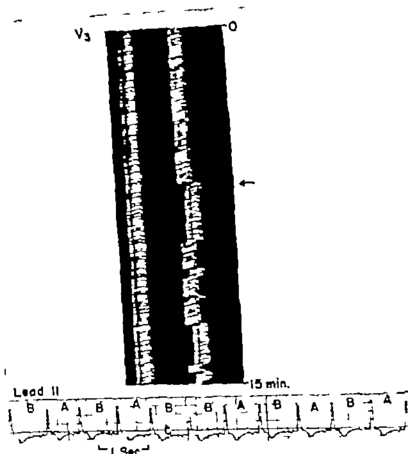


Fig. 7 Subtle trial bigeminy The contourograph (from a chest lead) triggers the tracing on the left margin, displaying two full cardiac cycles ith each horizontal sweep. Initially short cycle (A) precedes longer cycle (B). At point on the contourogram indicated by the arrow the long R R interval occurs on two consecutive beats and the contourographic sequence for each sweep is reversed from A B to B-A. The sum of consecutive intervals (A+B) is always the same, explaining the fact that the P and QS waves are perfectly lined p along the right margin of the contourograph regardless of which sequence has occurred.

cated Complex arrhythmias such as the varying second degree atrioventricular block in Fig 6 and the atrial bigeminy in Fig 7 could be identified on the contourogram However standard paper write-out was required for precise characterization of these arrhythmias.

The limitations are apparent from the earlier discussion Good information is dependent upon high-quality ECG signal close attention to electrode placement, maintenance of good contact, and avoid nce of interference are imperative. Certain arrhythmias such as widely varying R R intervals due to multifocal ectopic beats, are not adequately characterized (see Fig 3 panel A) Infrequently occurring ectopic beats will be detected correctly 100 per cent of the time (see Fig 8) Hence the type and timing of an arrhythmia determines whether the study of the contourogram will allow one to make a specific diagnosis (in contrast to determining that an arrhythmia has occurred) Therefore, we have made no systematic study to learn "how good contourography might be in detecting (for specific identification) arrhythmias since the result would be so heavily biased by the kind of arrhythmias studied

Exploratory studies have been done during the course of this work which ind cate that on-line" contourographic pro-

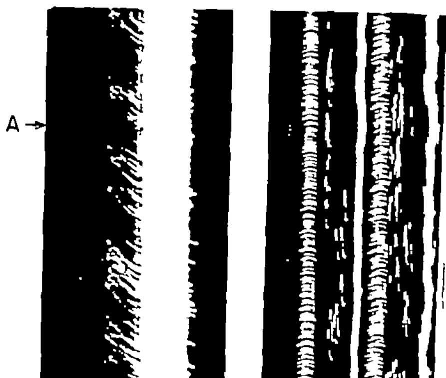


Fig 8 Vector loop modification. Ten minutes of standard Lead II ECG is shown on the right and the same data displayed as a vector-loop contourogram on the left. The standard technique reveals sinus rhythm with multiple ventricular premature contractions indentified by the upright slurred R waves scattered throughout the regular pattern of sinus rhythm. The vectorcardiogram on the left shows the small QRS-T loops of normal beats as a bright band down the center of the film the morphology of these loops is lost due to the intensity of the super imposed images. However each individual aberrant beat is easily identified by the larger wider more prolonged QRS-T loop with its considerably displaced mean QRS axis and divergent T axis. Point *A* demonstrates two ectopic beats from a second focus differing from the other aberrant beats by their loop of still another shape.

cessing utilizing paper recorders could give information similar to that which has been obtained by the photographic technique in this study The addition of timing and event markers is possible and would further enhance the usefulness of the technique.

Summary

Contourography is a technique to reduce large volumes of ECG data to a form which can be more easily reviewed More than 700 hours of taped ECG information from patients with acute ischemic episodes have been reviewed and the advantages and limitations of the method examined

Gross changes in cardiac rate rhythm and wave form are easily identified The contourographic technique is useful in demonstrating *abrupt or phasic changes in* cardiac rate and rhythm occurring on a steady-state background demonstrating trend changes and identifying data which should be subjected to more detailed analysis ECG wave form changes can usually be identified

Modifications to increase the usefulness of the method and the potentiality for on line processing of the information are considered

The authors wish to acknowledge the helpful advice and suggestions of Drs. Richard S. Ross, Richard J Johns, and William H Guier during the course of this work.

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Experimental and laboratory reports

A comparison of the cardiovascular actions of four adrenergic β-receptor blocking agents in resting, conscious dogs

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During the last ten years several compounds which block adrenergic β receptors have been developed and the actions of individual β adrenoreceptor blocking agents on the cardiovascular system have been extensively studied on isolated heart preparations and in anesthetized animals.[1-10] Nevertheless, the possibility of extrapolating the results obtained from the use of anesthetized animals to man is unfortunately limited by the evidence that anesthetic agents alter the function of the autonomic nervous system [11] The observation that contrary to the findings in anesthetized dogs [12-14] propranolol does not decrease coronary blood flow in these animals when they are in a conscious, resting state[15] further supports this evidence Therefore because these drugs are used for the treatment of cardiac disorders in man we feel that it is important that their effects on coronary and systemic hemodynamics be clearly defined in conscious trained animals.

Moreover because adrenergic β receptor blocking drugs may possess additional properties [16,17] a comparison of the actions of a selected group of drugs is necessary to elucidate the contribution of these properties to the effects of any individual compound such a comparison has not previously been made in conscious animals.

In this paper the effects of propranolol MJ 1999 (Sotalol) H 56/28 (Alprenolol) and I C I 50172 (Eractolol) on the coronary and systemic hemodynamics in resting conscious dogs are described

Methods

The experiments were performed on seven dogs weighing between 13 and 15 kilograms. Each dog was trained to lie quietly while observations were being made All operations were performed under sterile conditions while the animals were anesthetized with thiopentone (30 mg per kilogram intravenously) After the chest had been opened through the fourth left intercostal space artificial respiration was instituted with a mixture of oxygen and halothane (2 per cent) delivered from Bird Mark 4 and Bird Mark 8 respirators.

The pericardium was opened and the left circumflex coronary artery was care

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fully dissected free from surrounding tissues near its origin from the main trunk an electromagnetic flowmeter probe (Biotronex Lab) was implanted on the artery A pneumatic occlusive cuff was placed around the artery a few millimeters distal to the coronary flow transducers. Inflation of this cuff allowed the temporary occlusion of the artery in order that mechanical flow zeros could be obtained postoperatively[11] A larger electromagnetic flowmeter probe was implanted on the ascending aorta which had been previously cleaned of all adherent tissues. Aortic flow zero was taken as the position of the flow curve in late diastole. All tubes and cables were brought out through the chest incision the chest wall was closed in layers, and the pneumothorax was evacuated The flowmeter cables and pneumatic cuff tube were tunneled subcutaneously to the retroscapular region where they were attached to the skin A plastic catheter filled with physiological saline solution was then inserted through the left common carotid artery into the aorta to the level of the origin of the brachiocephalic artery The external end of the catheter was led out through the skin of the back. Subsequently the exact position of the tip of the catheter inside the aorta was checked radioscopically (Philips BW 20 S) The aortic catheter was flushed daily and refilled with saline solution only

Penicillin was given routinely preoperatively and daily thereafter for 5 to 7 days. Hemodynamic measurements were not made on the dogs until they had completely recovered from surgery (about 15 days)

Intravenous injections were given through a catheter acutely inserted into the cephalic vein of either foreleg The largest volume of fluid injected intravenously was 1 *ml* per kilogram and this was infused slowly over a period of 1 minute. An equal volume of saline given before treating the animals with the beta blockers, did not cause any change in the recorded cardiovascular parameters. During each experiment phasic aortic pressure was recorded by connecting the aortic catheter to a strain gauge transducer (Statham P 23 Db) the electrocardiogram (ECG) and phasic blood flow through the aorta and the left circumflex coronary artery were recorded on an eight channel Beckman type R Dynograph Stroke flows were measured by planimetry of the respective areas beneath the phasic flow patterns on a number of cardiac cycles. Mean blood pressure was obtained by electrical integration. Vascular resistance was calculated by the ratio between arterial pressure (in millimeters of mercury) and blood flow (in milliliters per minute) and expressed in peripheral resistance units (P.R.U.) late diastolic and late systolic resistances were calculated from the ratios of late diastolic and systolic pressures (in millimeters of mercury) to coronary flow at the same moment (in milliliters per minute) Left ventricular work (in kilogram meters per unit of time) was calculated as the product of cardiac output (in liters per minute) and the mean aortic pressure expressed in meters of water The heart rate was calculated from the time interval between successive heart beats.

The results obtained in all the parameters included in the tables were submitted to an analysis of variance which was carried out by using a two-way cross classification differences between groups (control 0 minute control 30 minutes, 0.2 and 1 0 mg per kilogram of the drugs) and between dogs. The data obtained from the four dogs which were treated with 0.04 mg per kilogram administered intravenously were calculated separately by comparing the results with their own controls.

The following drugs were used (1) isoprenaline (Aleudrin, C. H Boheringer & Sohn, Ingelheim) (2) propranolol (Inderal Imperial Chemical Industries [I C I.] Ltd) (3) MJ 1999 (Sotalol Mead Johnson, Ltd) (4) H 56/28 (Alprenolol Aptin, A. B Hassle) and (5) I C I 50172 (Practolol Eraldin I C I) All drugs were dissolved in sterile saline solution and the doses are expressed in terms of the salt. Dilutions of isoprenaline were made from the commercial stock solution.

Results

Control data. The general pattern of the aortic pressure, stroke volume, and left circumflex coronary inflow curves taken from seven dogs was basically similar in

*We are indebted to A. B. Hassle for H 56/28, to Mead Johnson for MJ 1999, and to I.C.I. for I.C.I 50172 and [illegible]

Table I *Effects of propranolol 0 04 to 0 2 and 1 mg per kilogram given by intravenous injectio... are the averaged results recorded 5 minutes after the injections with standard errors of the mea...*

No. of dogs	Dose (mg./Kg.)	Time (min.)		Heart rate (beats/min.)	Aortic blood pressure (mm. Hg)	Stroke volume (ml.)	Cardiac output (ml./min.)	Total peripheral resistance (P.R.U.)
		Before drug	After drug					
7	Control	30		114 ±8 03	99 ± 91	23 ±2 48	2 532 ±78	0 039 ±0 002
7	Control	0		113 ±6 90	100 ±2 61	23 ±2 45	2 49 ±154	0 037 ±0 002
4	Propranolol, 0 01		5	104 ±6 95	96 5 ±1 81	22 ±0 5 P < 0 01	256 ±77 P < 0 01	0 043 ±0 005 P < 0 05
7	Propranolol 0 20		5	103 ±5 52 P < 0 05	103 ±2 10	22 ±2 69 P < 0 01	2 238 ±161 P < 0 01	0 047 ±0 003 P < 0 01
7	Propranolol 1 0		5	106 ±6 28	100 ±3 01	21 ± 23 P < 0 01	153 ±178 P < 0 01	0 048 ±0 004 P < 0 01
Between controls		0 vs. 30 (min.)		P > 0 05	P > 0 05	P > 0 05	P > 0 05	P > 0 05

P values for 0.04 mg. per kilogram are calculated by comparing the results from the four dogs with their own controls. Where not indicat...

all dogs studied (Figs. 1 2 and 3) and to those previously described by Gregg and his collaborators.[18] Individual dogs had different heart rates with the control values being in the range of 60 to 130 beats per minute. The average value from all seven dogs was 108 ± 8 87 beats per minute (Tables I II III and IV) The average value of mean aortic pressure for the seven dogs was 98 ± 4 04 mm Hg Control cardiac output varied from 2 500 to 3 000 ml per minute with an average stroke volume of 25 ml The average volume of coronary blood flow during systole (0 09 ml) was about 21 per cent of that during diastole (0 43 ml) with considerable variation between different dogs at different times. There was no significant difference between the two control values of any of the parameters.

Propranolol The effect of intravenous administration of propranolol was studied in seven dogs. After control observations, propranolol 0 04 mg per kilogram was administered 30 and 60 minutes after the first injection the drug was given in doses of 0 2 and 1 mg per kilogram respectively (Table I and Fig 1) The first dose of propranolol reduced heart rate stroke volume, cardiac output and left ventricular work and increased total peripheral resistance with the exception of heart rate and aortic pressure, all changes were significant. Stroke and mean coronary flow were unchanged but end-diastolic coronary resistance was increased (P < 0 01) The administration of propranolol 0 2 mg per kilogram produced no further changes in any of the parameters except total peripheral resistance which was increased After administration of 1 mg per kilogram of propranolol there was a small but significant decrease in coronary blood flow and an increase in end-diastolic resistance The former change was also significant when compared to the value ob-

ng values of some cardiovascular parameters of conscious dogs (the values given in the table values)

Left ventricular work (...M./min.)	Coronary blood flow				Resistance	
	Mean (ml./min.)	Phasic			Mean (P.R.U.)	End-diastolic (P.R.U.)
		Systolic (ml.)	Diastolic (ml.)	Stroke (ml.)		
3 43 ±0 13	56 ±3 70	0 08 ±0 01	0 43 ±0 06	0 53 ±0 07	1 82 ±0 16	1 43 ±0 09
3 71 ±0 30	56 ±3 73	0 09 ±0 01	0 43 ±0 04	0 52 ±0 05	1 64 ±0 12	1 49 ±0 10
2 99 ±0 26 P < 0 05	53 ±4 69	0 05 ±0 003	0 48 ±0 05	0 51 ±0 04	1 78 ±0 16	1 63 ±0 17 P < 0 01
3 12 ±0 23 P < 0 05	57 ±4 43	0 10 ±0.01	0 48 ±0 04	0 58 ±0 03	1 89 ±0 18	1 70 ±0 11 P < 0 01
2 96 ±0 31 P < 0 01	61 ±4 0 P < 0 05	0 08 ±0 009	0 41 ±0 05	0 50 ±0 06	2 03 ±0 13 P < 0 05	1 76 ±0 09 P < 0 01
P > 0 05	P > 0 05	P > 0 05	P > 0 05	P > 0 05	P > 0 05	P > 0 05

0.05.

tained after administration of 0 2 mg per kilogram of the drug

MJ 1999 MJ 1999 administered in doses of 0 04 0.2 and 1 mg per kilogram was less effective than propranolol on the systemic parameters (see Table II) Significant changes in heart rate, cardiac output and total peripheral resistance were recorded only after the highest doses used at which time left ventricular work was unaltered. The changes in coronary flow and resistance induced by MJ 1999 were similar to those observed after propranolol

H 56/28 The changes in resting hemodynamics of seven conscious dogs induced by the three doses of H 56/28 were significantly different from those induced by propranolol (Fig 2 and Table III) Heart rate and cardiac output were increased while total peripheral resistance decreased left ventricular work was unchanged There were also differences in the response of the coronary circulation to H 56/28 mean coronary flow was unaltered while end diastolic resistance was significantly decreased.

I C.I 50172 Although I C.I 50172 produced no changes in heart rate aortic pressure, cardiac output, or left ventricular work, it had a biphasic dose-dependent effect on coronary hemodynamics (see Table IV and Fig 3) Diastolic, stroke, and mean coronary flow were significantly increased by the smallest dose of the drug (0.04 mg per kilogram intravenously) while end-diastolic coronary resistance was unaltered The same parameters were significantly reduced by the largest dose of I C I 50172 (1 mg per kilogram)

Effect of drugs on responses to isoprenaline

Figs. 4 and 5 show the maximum effects of the intravenous injection of isoprenaline 0.2 mg per kilogram on sys

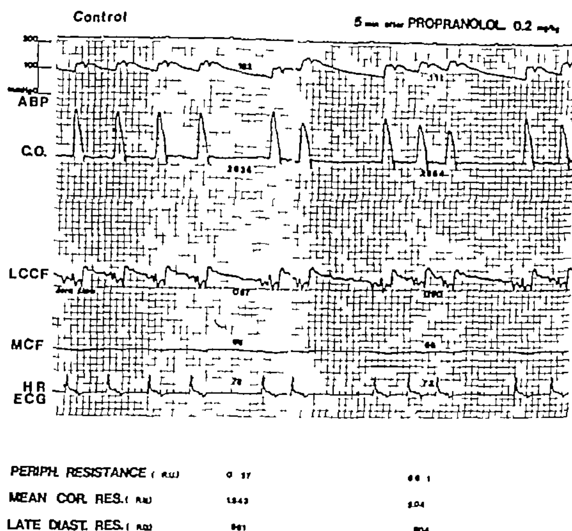


Fig. 1. Records obtained before (control) and 5 minutes after the intravenous injections of 0.2 mg. per kilogram of propranolol. Symbol *ABP* = aortic blood pressure numbers indicate mean pressure (mm. Hg) *CO* = cardiac output (ml./min.) *LCCF* = phasic left circumflex coronary flow numbers indicate the stroke flow (ml.) *MCF* = mean coronary flow (ml./min.) *HR* = heart rate (beat/min.) *ECG* = electrocardiogram Lead II

temic and coronary hemodynamics. Isoprenaline increased heart rate stroke volume and cardiac output while decreasing peripheral systemic resistance and aortic pressure Mean coronary blood flow was *markedly increased as a result of increase* in both stroke systolic and diastolic flow mean and late diastolic coronary resistance were markedly decreased The influence of the four beta blockers on the maximum changes produced by isoprenaline has been compared and the result of a typical experiment is given in Fig 4 Observations were made in four dogs for each drug In each dog isoprenaline was injected at least twice before and then 5 minutes after each dose of the β *adrenergic receptor* blocking drug

Propranolol Doses of 0 04 0 2 and 1 mg per kilogram of propranolol reduced the effect induced by isoprenaline on coronary and systemic hemodynamics of conscious dogs. The changes in heart rate cardiac *output, and left ventricular* work were almost completely blocked after 0 2 mg per kilogram of the drug the increases in mean and stroke coronary flows, and the decreases in end-diastolic resistance were also effectively inhibited by the same dose of propranolol (see Figs. 4 and 5)

MJ 1999 The results obtained after intravenous injection of MJ 1999 were similar to those observed after propranolol 0 2 mg per kilogram of the compound completely blocked the changes in heart rate cardiac output left ventricular work total

CONTROL H 56/28 0.04 mg/kg 0.2 mg/kg 1 mg/kg

HR ECG

ABP

C.O.

LCCF

TPR

MCR

LDR

Fig. 2. Records obtained during control period and 5 minutes after the intravenous i jections of 0.04 0.2, and 1 mg per kilogram of H 56/28. The numbers over the phasic coronary flow curves indicate mean flow (ml./min.) the numbers included i the same curves indicate stroke coronary flow (ml.) *TPR* = total peripheral resistance *MCR* and *LDR* = mean and late coronary resistance other symbols as in Fig. 1.

C t l fter I.C.I. 50172 0.04 mg/kg 0.2 mg/kg 1 mg

ABP

C.O.

LCCF

MCF

HR ECG

TPR

MCR

LDR

Fig. 3 Records obtained before (control) and 5 minutes after the intra...
mg. per kilogram of I.C.I. 50172 ...

Table II Effects of MJ 1999 0 04 to 0 2 and 1 mg per kilogram given by intravenous injection

No. of dogs	Dose (mg./Kg.)	Time (min.)		Heart rate (beats/min.)	Aortic blood pressure (mm. Hg)	Stroke volume (ml.)	Cardiac output (ml./min.)	Total peripheral resistance (P.R.U.)
		Before drug	After drug					
7	Control	30		114 ±9 4	93 ±5 02	23 ±3 40	3 047 ±165	0 033 ±0 003
7	Control	0		114 ±8 85	101 ±3 1	27 ±3 23	2 892 ±201	0 037 ±0 003
4	MJ 1999 0 01		5	103 ±13 4	105 ±3 9	27 ±4 7	2 693 ±209	0 040 ±0 005
7	MJ 1999, 0 20		5	109 ±6 70	100 ±3 04	26 ±3 25	2 44 ±253	0 035 ±0 004
7	MJ 1999 1 0		5	101 ±5 84 $P < 0.01$	104 ±5 17	26 ±3 18	2 547 ±167 $P < 0.01$	0 041 ±0.003 $P < 0.01$
Between controls		0 vs. 30 (min.)		$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$

peripheral resistance The changes in the coronary circulation were markedly reduced by this dose but there was little further change after administration of 1 mg per kilogram (see Fig 5)

H 56/28 H 56/28 was more effective than propranolol in antagonizing the cardiovascular responses to isoprenaline The lowest dose of H 56/28 (0 04 mg per kilogram) almost completely blocked the hemodynamic effects of isoprenaline. No further change in the absolute responses occurred after the two larger doses (see Fig 5)

I C I 50172 I C I 50172 reduced the changes in heart rate cardiac output and left ventricular work caused by isoprenaline to a lesser degree than did propranolol the changes in total peripheral resistance and in mean and late diastolic resistance were unaltered Even after the largest dose of I C.I 50172 there were still marked responses in all parameters to isoprenaline (see Fig 5)

Discussion

The present observations were made in conscious dogs when they were under the influence of no drugs and in a normal healthy condition As they were trained to lie quietly observations were generally made when they were in a resting state. In this way the effects of drugs (e g barbiturates) of changes in intrathoracic pressure due to thoracotomy [7,8,18-21] and of alterations in activity of the autonomic nervous system on the heart and circulation were reduced to a minimum [11,21,22] In the present experiments propranolol and MJ 1999 had little effect on systemic hemodynamics. Heart rate was practically unaltered while cardiac output was slightly decreased which resulted in a decrease in the external work of the left ventricle

The difference between the results of the present study and those previously reported from anesthetized dogs[8] can be ascribed to the increase in activity of the β-sympathetic receptors during anes

resting values of some cardiovascular parameters of conscious dogs (averaged results from seven dogs)

Left ventricular work (*Kg-M./min.*)	*Coronary blood flow*				*Resistance*	
	Mean (*ml./min.*)	*Phasic*			*Mean* (*P.R.U.*)	*End-diastolic* (*P.R.U.*)
		Systolic (*ml.*)	*Diastolic* (*ml.*)	*Stroke* (*ml.*)		
4.04 ±0.[illegible]	61 ±5.43	0.09 ±0.01	0.46 ±0.05	0.55 ±0.06	1.65 ±0.10	1.46 ±0.13
3.90 ±0.36	63 ±6.61	0.09 ±0.008	0.47 ±0.05	0.56 ±0.07	1.74 ±0.18	1.63 ±0.15
3.84 ±0.20	57 ±7.83	0.09 ±0.03	0.46 ±0.09	0.55 ±0.11	1.97 ±0.20 P < 0.05	1.64 ±0.20
3.73 ±0.36	58 ±6.59	0.10 ±0.03	0.43 ±0.04	0.53 ±0.05	1.90 ±0.15	1.73 ±0.16 P < 0.05
3.48 ±0.27	64 ±5.97 P < 0.05	0.10 ±0.01	0.44 ±0.04	0.54 ±0.06	2.02 ±0.17 P < 0.01	1.99 ±0.18 P < 0.01
P > 0.05	P > 0.05	P > 0.05	P > 0.05	P > 0.05	P > 0.05	P > 0.05

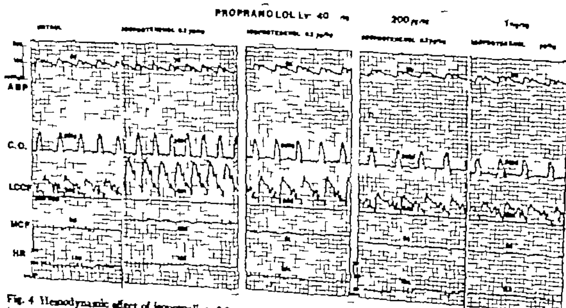


Fig. 4. Hemodynamic effect of isoprenaline, 0.2 μg per kilogram intravenously before and 5 minutes after the intravenous injections of 0.04, 0.2, and 1 mg per kilogram of propranolol. Symbols as in Fig. 1.

Table III Effects of H 56/28 0 04 to 0.2 and 1 mg per kilogram given by intravenous injection in

No. of dogs	Dose (mg./Kg.)	Time (min.)		Heart rate (beats/min.)	Aortic blood pressure (mm. Hg)	Stroke volume (ml.)	Cardiac output (ml./min.)	Total peripheral resistance (P.R.U.)
		Before drug	After drug					
7	Control	30		103 ±10 25	95 ±4 78	27 ±2 72	663 ±211	0 036 ±0 003
7	Control	0		108 ±10 90	90 ±4 08	[illegible] ± 43	502 ±230	0 037 ±0 004
4	H 56/28, 0 04		5	118 ±8 6	98 ±7 0	26 ±3 0	3 016 ±459	0 036 ±0 008
7	H 56/28, 0 20		5	119 ±7 09	90 ±4 02	25 ±2 9 0 01 < P < 0 05	553 ±224	0 034 ±0 004
7	H 56/28 1 0		5	134 ±10 38 P < 0 01	90 ±3 32	4 ± 37 P < 0 01	3 142 ±273	0 031 ±0 004 0 01 < P < 0.05
Between controls Regression		0 vs. 30 (min.) 0.2 vs. 1.0 (mg./Kg.)		P > 0 05 P > 0 05	P > 0 05 P > 0 05	P > 0 05 P > 0 05	P > 0 05 P > 0 05	P > 0 05 P > 0 05

Table IV Effects of I C I 50172 0 04 to 0 2 and 1 mg per kilogram given by intravenous injection

No. of dogs	Dose (mg./Kg.)	Time (min.)		Heart rate (beats/min.)	Aortic blood pressure (mm. Hg)	Stroke volume (ml.)	Cardiac output (ml./min.)	Total peripheral resistance (P.R.U.)
		Before drug	After drug					
7	Control	30		104 ±7 73	96 ±4 93	4 ±2 59	440 ±173	0 041 ±0 004
7	Control	0		101 ±8 85	96 ±4 77	25 ±2 90	2 371 ±150	0 042 ±0 004
4	I.C.I. 50172, 0 04		5	108 ±7 03	102 ±5 75	4 ±2 86	2 545 ±337	0 042 ±0 006
7	I.C.I. 50172, 0 20		5	104 ±6 91	97 ±3 27	4 ±3 33	2 436 ±267	0 044 ±0 007
7	I.C.I. 50172, 1 0		5	106 ±4 68	96 ±3 74	1 ± 92	2 491 ±282	0 042 ±0 007
Between controls Regression		0 vs. 30 (min.) 0.2 vs. 1.0 (mg./Kg.)		P > 0 05 P > 0 05	P > 0 05 P > 0 05	P > 0 05 P > 0 05	P > 0 05 P > 0 05	P > 0 05 P > 0 05

resting values of some cardiovascular parameters of conscious dogs (averaged results from seven dogs)

Left ventricular work (Kg. M./min.)	Coronary blood flow				Resistance	
	Mean (ml./min.)	Phasic			Mean (P.R.U.)	End-diastolic (P.R.U.)
		Systolic (ml.)	Diastolic (ml.)	Stroke (ml.)		
3.40 ±0.43	49 ±4.06	0.09 ±0.01	0.40 ±0.05	0.49 ±0.05	2.02 ±0.17	2.1 ±0.30
3.77 ±0.38	51 ±4.40	0.10 ±0.01	0.40 ±0.06	0.50 ±0.06	2.0 ±0.14	2.02 ±0.21
3.65 ±0.60	52 ±7.20	0.09 ±0.01	0.34 ±0.07 0.01 < P < 0.05	0.43 ±0.04 0.01 < P < 0.05	1.96 ±0.20	2.03 ±0.30
3.84 ±0.27	51 ±5.08	0.10 ±0.01	0.34 ±0.03 P < 0.01	0.43 ±0.04 0.01 < P < 0.05	2.06 ±0.22	1.72 ±0.21
3.84 ±0.33	53 ±8.30	0.10 ±0.01	0.29 ±0.03 P < 0.01	0.38 ±0.04 P < 0.01	1.92 ±0.23	1.62 ±0.23 0.01 < P < 0.05
P > 0.05 P > 0.05	P > 0.05 P > 0.05	P > 0.05 P > 0.05	P > 0.05 P > 0.05	P > 0.05 P > 0.05	P > 0.05 P > 0.05	P > 0.05 P > 0.05

on resting values of some cardiovascular parameters of conscious dogs (averaged results from seven dogs)

Left ventricular work (Kg. M./min.)	Coronary blood flow				Resistance	
	Mean (ml./min.)	Phasic			Mean (P.R.U.)	End-diastolic (P.R.U.)
		Systolic (ml.)	Diastolic (ml.)	Stroke (ml.)		
3.16 ±0.22	56 ±5.63	0.10 ±0.01	0.47 ±0.07	0.56 ±0.08	1.85 ±0.29	1.82 ±0.36
3.08 ±0.21	57 ±7.43	0.10 ±0.02	0.50 ±0.09	0.60 ±0.10	1.90 ±0.32	1.63 ±0.22
3.45 ±0.36	67 ±6.43 0.01 < P < 0.05	0.11 ±0.003	0.51 ±0.07 0.01 < P < 0.05	0.62 ±0.07 0.01 < P < 0.05	1.68 ±0.20	1.92 ±0.34
3.10 ±0.29	54 ±6.19	0.09 ±0.01	0.45 ±0.06	0.54 ±0.09	1.96 ±0.26	1.78 ±0.29
3.29 ±0.[illegible]	49 ±5.61 0.01 < P < 0.05	0.08 ±0.05	0.39 ±0.06 P < 0.01	0.47 ±0.07 P < 0.01	2.15 ±0.31 0.01 < P < 0.05	1.94 ±0.26
P > 0.05 P > 0.05	P > 0.05 P > 0.05	P > 0.05 P > 0.05	P > 0.05 0.01 < P < 0.05	P > 0.05 0.01 < P < 0.05	P > 0.05 P > 0.05	P > 0.05 P > 0.05

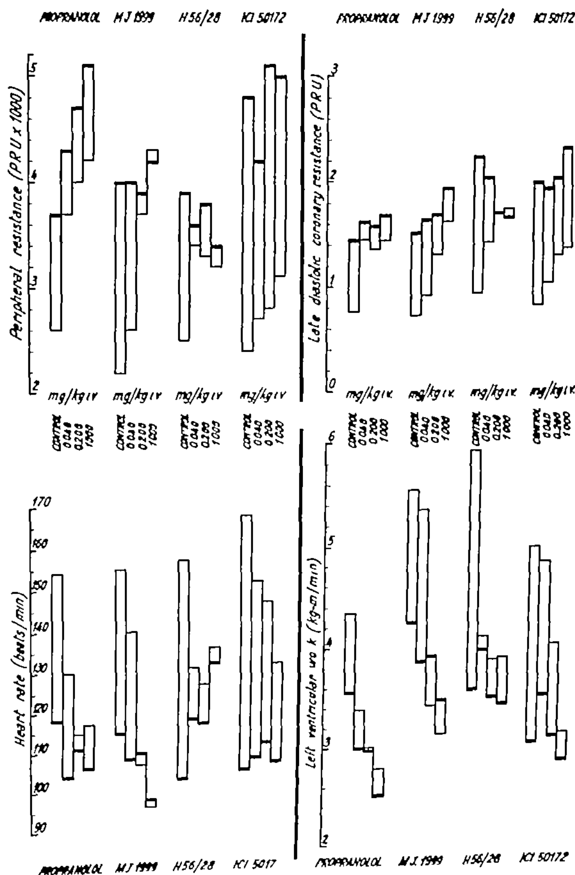


Fig 5 Effects of the intravenous injection of three doses of propranolol MJ 1999 H 56/28 and I C I 50172 on the changes in peripheral resistance heart rate, late diastolic coronary resistance and left ventricular work. Averaged results from four conscious dogs for each drug The double bar denotes the resting value and the single bar the maximum response to isoprenaline.

thesia.[11] Propranolol and MJ 1999 were equipotent in blocking the increases in heart rate and left ventricular work produced by isoprenaline. Previous studies in anesthetized dogs[16] have shown that propranolol is five to ten times more potent than MJ 1999 in blocking the cardiovascular effects of isoprenaline the reason for the difference between earlier reports and the present observations is not clear

H 56/28 and I C I 50172 have been shown to possess intrinsic sympathomimetic activity since they increase heart rate in anesthetized cats pretreated with either reserpine[7] or syrosingopine. In the present experiments *H 56/28 also increased* heart rate (28 per cent) and cardiac output (14 per cent) while it decreased total peripheral resistance in contrast I C.I 50172 did not alter any of the systemic parameters in conscious dogs.

H 56/28 had comparable activity to propranolol and MJ 1999 in blocking the response to isoprenaline, but an accurate comparison could not be made, as it altered the resting values through its intrinsic sympathomimetic activity

Although I C I 50172 reduced the isoprenaline induced tachycardia, its effect was less than that of any of the other β-receptor blocking drugs. While it was effective in blocking the increase in left ventricular work this compound had little effect on the reduction in total peripheral resistance produced by isoprenaline. Similar results have been described previously in which I C.I. 50172 was shown to selectively block adrenergic β-receptors in the heart but not in the vasculature.[8] Due to its peculiar mode of action it is difficult to compare the β-receptor blocking activity of I C I 50172 with that of the other drugs on the cardiac responses to isoprenaline. Previous studies[8] have already indicated that I C.I. 50172 has one third to one fourth the potency of propranolol in blocking the cardiac actions of isoprenaline.

In the present experiment propranolol and MJ 1999 slightly decreased mean coronary flow (9 and 11 per cent respectively) while they had no effect on stroke systolic and stroke diastolic coronary blood flow These observations are in contrast to those reported by others who showed in anesthetized dogs, often with thoracotomy that propranolol reduced coronary blood flow [11, 14, 15] However our results agree with those reported by Pitt and co-workers,[12] who found no change in coronary blood flow in conscious dogs after administration of propranolol In anesthetized animals where sympathetic activity is high propranolol has a negative inotropic action and the reduction in coronary blood flow may be attributed to a decrease in the oxygen requirement of the heart. In conscious resting dogs a close relationship between left ventricular work, mean coronary blood flow and cardiac oxygen consumption has been established [20] The present results indicate *that under similar experimental conditions* propranolol and MJ 1999 reduce the cardiac oxygen requirement.

Mean coronary flow also was unaltered by H 56/28 because the increase in heart rate was paralleled by a decrease in stroke diastolic flow The smallest dose of I C I 50172 increased mean coronary flow while it was decreased significantly by the largest dose. The increase in coronary flow may be due to a sympathomimetic action of the drug which is lost when larger amounts are given.

The action of the four β adrenoreceptor blocking agents on coronary blood vessels is reflected by the changes in end-diastolic resistance, as it has been suggested that the pressure-flow relationship determined at the end of diastole is an index of the changes in caliber of the coronary arterioles.[14]

Propranolol and MJ 1999 slightly increased end-diastolic resistance, whereas it was unaltered by I C I 50172 and decreased by H 56/28 The increase in resistance produced by the two former drugs probably is the result of blockade of tonic activation of adrenergic β-receptor in the coronary arterioles,[23] thereby unmasking the activity of adrenergic constrictor receptors in the coronary arteries. The intrinsic sympathomimetic activity of H 56/28 may overcome this action, so that there is a decrease in resistance after this drug

Propranolol, MJ 1999 and H 56/28 were almost equipotent in blocking the effect of isoprenaline on coronary circulation I C.I 50172 was less potent. On the basis of reduction in coronary blood flow induced by propranolol in anesthetized dogs, it has

been suggested that a similar effect may occur in man and that this may be dangerous.[14,24,25] The present observations in conscious dogs indicate that β receptor blocking agents have little effect on coronary circulation and on systemic hemodynamics when the animals are in resting condition. Our results also suggest that the trained conscious dog is a reliable model for the study of the action of drugs on the cardiovascular system.

Summary

The present study was undertaken to investigate the effect of blockade of adrenergic β receptors on resting hemodynamics in conscious dogs. Contrary to the findings in anesthetized animals in which the activity of the autonomic nervous system is markedly altered, propranolol and MJ 1999 had little effect on heart rate, cardiac output, and left ventricular work. These two drugs were also equipotent in blocking the cardiovascular effects induced by isoprenaline. H 56/28 and I C I 50172 have been shown to possess intrinsic sympathomimetic activity; in the present experiments H 56/28 also increased heart rate and decreased total peripheral resistance. I C I 50172 did not alter the systemic hemodynamics in conscious dogs. H 56/28 had comparable activity to propranolol and MJ 1999 in blocking the response to isoprenaline while I C I 50172 was less potent.

In contrast with the earlier observations that β receptor blocking agents markedly decrease coronary flow in anesthetized animals, propranolol, MJ 1999, and H 56/28 had practically no effect on resting coronary circulation in conscious dogs. All three drugs increased coronary resistance and were almost equipotent in blocking the effect of isoprenaline on coronary hemodynamics. I C I 50172 had a biphasic dose-dependent effect: the coronary flow was increased by the smallest dose and decreased after the largest one. This compound had no effect on late diastolic resistance and was less potent than the other three drugs in antagonizing the coronary changes induced by isoprenaline.

The present observations indicate that β receptor blocking agents have little effect on the coronary circulation and systemic hemodynamics and suggest that it could be misleading to extrapolate the findings in anesthetized dogs to man.

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Ventricular endocardial potentials after experimental coronary artery occlusion in dogs

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Low right ventricular endocardial potentials (RVECP) in patients with acute myocardial infarction have been previously reported [1,2] but the mechanisms remain unexplained It is not known for example whether the low ECP is due to the electrode being in contact with ischemic endocardium or not Furthermore the behavior of left ventricular endocardial potential (LVECP) and its relation to RVECP following coronary artery occlusion are also not known In the clinical study an apparent relationship was noted between the degree of fall of RVECP and the severity of clinical heart failure but no hemodynamic measurements were performed to verify this clinical impression

The present study was designed to investigate, in dogs, the behavior of both right and left ventricular endocardial potentials and their relation to hemodynamic alterations following experimental complete coronary artery occlusion

Methods

Nine beagle dogs, 9 5 to 13 2 kilograms in body weight were anesthetized with intravenous pentobarbitone (30 mg per kilogram) and their respiration was maintained mechanically by a positive pressure respirator (Palmer Starling Respirator) The chest was opened by midsternotomy in one dog and by left thoracotomy through the fifth intercostal space in eight dogs. The heart was exposed by excising the pericardium For recording endo- and epicardial potentials, hook electrodes made of Nichrome wires (8/1 000 inch diameter) were used The whole length of the electrodes, except at the tip in the case of endocardial and at the angle of the hook in the case of epicardial electrodes were insulated with Diamel varnish The epicardial electrodes were attached to the superficial layers of the epicardium directly The endocardial electrodes were introduced into the ventricular cavity through a No 1 hypodermic needle and then gently withdrawn until the electrograms recorded showed characteristic ventricular intracavitary configuration with ST elevation contact pattern.[4] In all experiments unipolar potentials were recorded and in two experiments in addition bipolar potentials were also recorded simultaneously from the same sites. The approximate distance between

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the bipolar leads was 1/1 000th inch. Needle electrodes were used for recording standard Lead II electrocardiograms (ECG)

RVECPs were recorded from the inferior wall near the apex. LVECPs were recorded from two sites (1) the anterior wall in the left anterior descending artery territory (LVECP Ant.) and (2) the inferior wall in the left circumflex artery territory (LVECP Inf) Left ventricular epicardial potentials (LVEPP) were recorded from the anterior surface in the anterior descending artery territory (LVEPP Ant.) and from the inferior surface in the left circumflex territory (LVEPP Inf) No right ventricular epicardial potentials (RVEPP) were recorded A catheter tipped micromanometer* was introduced into the cavity of the left ventricle through its apex and the first derivative of left ventricular pressure pulse (LV dp/dt) was determined by electronic differentiation Aortic pressure was measured by left carotid artery cannulation. All parameters were recorded simultaneously on an eight channel tape recorder (Precision Instruments) and permanent records were subsequently obtained on an eight-channel paper recorder (Minograph 81)

The coronary artery to be ligated was first dissected and isolated near its origin and a cotton thread was placed loosely around it. After a control period of observation for 30 minutes, the artery was ligated and observations were continued for at least 60 minutes. At the end of the experiments, the animals were killed and the hearts were dissected to verify the positions of the endo- and epicardial electrodes. To delineate the ischemic areas, 15 to 20 c.c. of Coomassie Blue dye were injected at the root of the aorta in six dogs. After the animals had been killed and the hearts had been dissected well perfused areas were bright blue and the clearly unperfused areas remained gray Thus the ischemic (nondyed) and the nonischemic (dyed) areas could be identified on both the epicardial and endocardial surfaces of the ventricles. Histological examinations were not performed

The calibration voltage for the measurement of the potentials was chosen according to the amplitude of the potential The potential was defined as the total deflection of the QRS (without the ST) and the measurement taken was the average of ten complexes (ventricular premature beats were excluded) The control measurements of the potentials, LV dp/dt and mean aortic pressure (PAO) at 30 minutes before the ligation of the coronary arteries were regarded as 100 per cent and the changes at subsequent observations, both immediately before (0 minute) and after ligation (+10 20 30 40 50 and 60 minutes) were expressed as the percentage of the control values.

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Results

In six of the nine dogs the left circumflex artery (LCA) was ligated in two dogs the left main coronary artery (LMCA) was ligated in one dog the left anterior descending (LAD) artery was ligated. In eight dogs the postocclusion changes were recorded at ten-minute intervals up to 60 *minutes* in one animal ventricular fibrillation occurred 15 minutes after ligation of the LMCA, and in this dog the post occlusion changes were recorded only at ten minutes.

A typical example of changes in LVECP and LVEPP following occlusion of a coronary artery is shown in Fig 1

The percentage changes in the mean values of the potentials, LV dp/dt, and aortic pressures, both before and after ligation of the coronary arteries, are shown in Table I and Fig 2. Postocclusion changes in individual experiments are shown in Fig 3 The pre- and postocclusion potentials (in millivolts) are summarized in Table II

Endocardial potentials LVECP Ant. fell in all nine dogs following coronary artery occlusion (Fig 3 *a*) LVECP Inf., recorded in six dogs, fell in four and remained unchanged in two (Fig 3 *c*) RVECP recorded in seven dogs, fell significantly in four and remained unchanged in three (Fig 3 *e*) The mean postocclusion ECP remained lower than the control values throughout the period of observation (Table I) The fall in ECP when it occurred was not related to the coronary artery ligated (Table II)

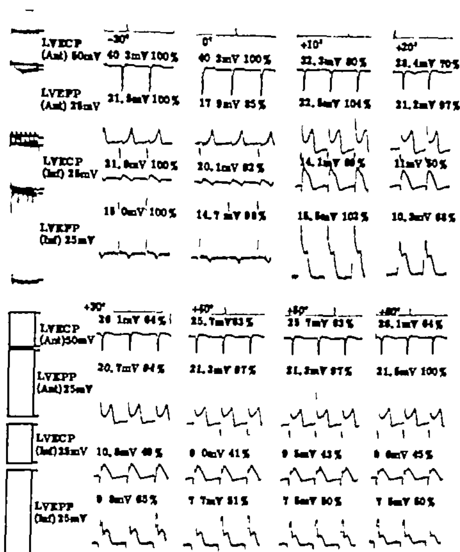


Fig. 1. Simultaneously recorded endo- and epicardial potentials from the anterior and inferior walls of the left ventricle both before and after circumflex artery occlusion. Both LVECP Ant. and LVECP Inf. fell following occlusion. Transient rise in epicardial potentials with appearance of the injury pattern followed by gradual fall is also shown.

LVECP Ant. was recorded in all six hearts that were examined by injection of dye to delineate ischemic areas. LVECP Inf. and RVECP were recorded only in five such hearts. Fall in LVECP Ant. was observed whether the electrodes were in ischemic (three hearts) or in nonischemic areas (three hearts). The endocardial electrodes for LVECP Inf. were in ischemic areas in four (in three a fall in LVECP Inf. occurred and in one no change was observed) and in nonischemic areas in one heart (no change in LVECP Inf. occurred). The electrodes for RVECP were in ischemic areas in two hearts, but only in one of these did a fall in RVECP occur. In the remaining three hearts the electrodes were in nonischemic areas and in two of these RVECP fell.

Bipolar potentials. Bipolar and unipolar potentials were recorded simultaneously in two dogs from the same sites. Although the bipolar potentials were smaller in amplitude than unipolar potentials the post occlusion changes were similar (Fig. 4).

Epicardial potentials. LVEPP Ant. were recorded in nine dogs and LVEPP Inf. in six. After ligation of the coronary artery the changes in epicardial potentials were variable. In most dogs there was an initial increase in epicardial potentials with the appearance of the injury pattern (monophasic potential and marked ST elevation) followed by a gradual fall (Figs. 1 and 2). At

*T ble I. Changes in potenti ls, LV dp/dt, and PAO after ligation of coronary rteries**

Time (min.)	LVECP (Ant.)	LVEPP (Ant.)	LVECP (Inf.)	LVEPP (Inf.)	RVECP	Lead II	LV dp/dt	PAO (mm Hg)
−30	100	100	100	100	100	100	100	100
0	101 ± 3.7	94.0 ± 14.0	99.5 ± 4.8	103 ± 7.4	101 ± 8.8	93 ± 9.0	102.9 ± 11.3	105 ± 10.5
+10	72.8 ± 11.3 P < 0.001	110 ± 29.8 0.10 < P < 0.20	87.8 ± 14.1 0.05 < P < 0.10	125 ± 30.0 0.05 < P < 0.10	79.1 ± 22.5 P 0.03	134 ± 64 0.10 < P < 0.20	68.5 ± 25.0 0.001 < P < 0.005	89 ± 8.8 0.10 < P < 0.20
+20	65.8 ± 16.0 P < 0.001	120 ± 20.0 0.01 < P < 0.05	79.8 ± 19.0 0.005 < P < 0.01	111 ± 34 0.50 < P < 0.60	85.6 ± 21.4 0.10 < P < 0.20	114 ± 85 0.30 < P < 0.90	62 ± 11.8 P < 0.001	58.3 ± 31.3 0.10 < P < 0.20
+30	63.1 ± 19.3 P < 0.001	127 ± 70.0 0.25 < P < 0.30	71 ± 18.7 0.001 < P < 0.005	111 ± 35 0.50 < P < 0.60	87.6 ± 28.1 0.05 < P < 0.10	118 ± 34 0.05 < P < 0.10	68.3 ± 21.7 0.001 < P < 0.005	82.0 ± 28.0 0.025 < P < 0.05
+40	64.0 ± 14.3 P < 0.001	133 ± 68.0 0.20 < P < 0.25	69.6 ± 28.6 0.025 < P < 0.05	107 ± 36 0.70 < P < 0.90	78.8 ± 21.1 0.01 < P < 0.03	130 ± 24 0.01 < P < 0.02	68.5 ± 21.3 0.001 < P < 0.005	88 ± 25.7 0.05 < P < 0.10
+50	61.6 ± 14.0 P < 0.001	105 ± 42.0 0.40 < P < 0.50	61.8 ± 25.8 0.005 < P < 0.01	93 ± 40 0.50 < P < 0.60	72.0 ± 30.2 0.025 < P < 0.05	134 ± 36 0.005 < P < 0.01	66 ± 24.8 P < 0.001	63.6 ± 31.4 0.10 < P < 0.20
+60	61.8 ± 14.6 P < 0.001	90.7 ± 26.8 0.50 < P < 0.60	64.3 ± 26.5 0.005 < P < 0.01	88 ± 30 0.20 < P < 0.25	82.5 ± 29.9 0.05 < P < 0.10	105 ± 29.9 0.30 < P < 0.40	66.6 ± 25.3 0.005 < P < 0.01	97 ± 21.0 0.20 < P < 0.25

*Values at 30 minutes before coronary artery occlusion were regarded as 100 per cent and the subsequent changes are expressed as percentage of these values. Statistical significance (P values) are also shown, along with standard deviation.

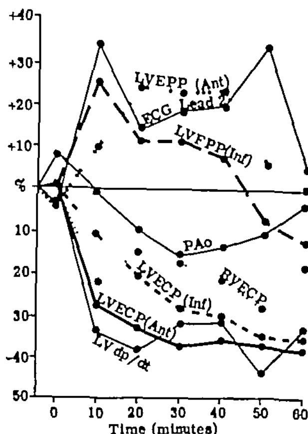


Fig 2 Percentage changes in mean values of potentials, LV dp/dt and PAO following ligation of the coronary arteries.

60 minutes LVEPP Ant was slightly increased in four dogs, slightly reduced in three and unchanged in two dogs as compared with control values (Table II Fig 3 *c*) Similarly LVEPP Inf at 60 minutes was reduced in four dogs and increased in two as compared with control values (Table II and Fig 3 *d*) The changes in epicardial potentials were not related to the coronary artery ligated No correlation was present between postocclusion percentage change of LVEPP Ant. and LVEPP Inf neither was there any correlation between changes in LVECP Ant. and LVEPP Ant. or LVECP Inf and LVEPP Inf In six hearts that were examined by injection of dye the epicardial electrodes on both the anterior and inferior walls of the left ventricle were in mottled areas whether the electrodes were in ischemic or nonischemic areas could not be precisely determined

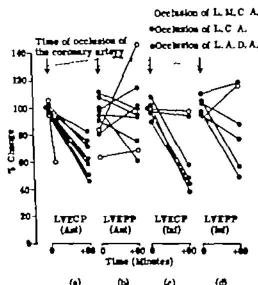
Potentials in Lead II Lead II ECGs recorded in seven of the nine dogs showed variable changes following ligation of the coronary arteries. QRS potentials increased initially in most dogs, with the appearance of the injury pattern (ST elevation) followed by a gradual fall of QRS potential (Fig 2) At 60 minutes it was slightly increased in four dogs, slightly reduced in two and unchanged in one (Table II) The changes in potentials were not related to the coronary artery ligated (Fig 3 *f*)

Rate of rise of LV dp/dt The changes in LV dp/dt were recorded in seven of the nine dogs. After ligation of the coronary arteries reduction occurred in all but one dog (Fig 2 *g*) The mean postocclusion reduction was significant at all periods of observation (Table I) The correlation between postocclusion changes in LV dp/dt and in LVECP and between LV dp/dt and RVECP are shown in Fig 5 Moderate but significant correlation was found between changes in LV dp/dt and LVECP (r = 0.568 P < 0.001) and between LV dp/dt and RVECP (r = 0.548 P < 0.001)

Changes in PAO were recorded in seven of the nine dogs there was an initial fall in five dogs and no significant change in two following ligation of the coronary arteries (Fig 3 *h*) In general the fall in PAO was not marked and in most dogs PAO returned almost to control level at 60 minutes after ligation of the coronary arteries. No correlation was found between the changes in PAO and changes in LVECP or RVECP

Discussion

The clinical observation that a fall in ventricular endocardial potentials may occur following acute coronary artery occlusion was confirmed in this study In all animals, during the control period of observation there was no change either in left or right ventricular endocardial potentials. Following ligation of the coronary arteries LVECP Ant fell in all animals and LVECP Inf and RVECP in most The fall in endocardial potential occurred soon after ligation and the values remained lower than the control values throughout the periods of observation The present study also demonstrated that postocclusion changes in endocardial potentials recorded simultaneously from the two ventricles or from the different sites of the same ventricles may vary In Dogs 4 (LC ligated) and 5 (LMC ligated) LVECP Ant. fell but no changes were observed in LVECP Inf or RVECP



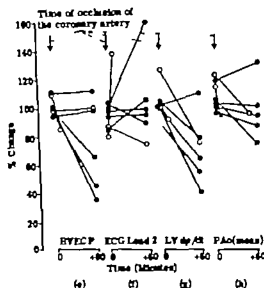


Fig. 3. Changes in individual experiments at 60 minutes after ligation of the coronary arteries, potentials (a to f) LV dp/dt (g) and mean PAO (h).

(Table II). The explanation for this difference remains obscure but it is unlikely to be due to the cancellation of the potentials at the two surfaces of the ventricle as no reciprocal relation was found between LVECP Ant. and LVECP Inf. (Fig. 6).

The changes in ECP in this study could not be attributed to electrode position in relationship to ischemic or nonischemic endocardium (Fig. 7). In six hearts examined with injection of dye to delineate ischemic and nonischemic endocardium the endocardial electrodes at the anterior wall of LV were in ischemic areas in three and in nonischemic areas in the other three, but LVECP Ant. fell in all. In two of the same six hearts, however, where LVECP Inf. and RVECP were also recorded simultaneously with LVECP Ant., no fall occurred in LVECP Inf. in one and in RVECP in the other, although the endocardial electrodes were in contact with ischemic endocardium. The explanation of this lack of change in ECP recorded from the ischemic area remains obscure. Hellerstein and Katz,[8] while investigating electrical effects of experimental myocardial injury in dogs, also reported in some animals no alteration in QS complexes recorded from a subjacent electrode within the right ventricular cavity after local coagulation of a large area of the anterior wall of the right ventricle.[7] Hence, although the relationship between localized myocardial ischemia or infarction and fall of ECP remains uncertain, these findings suggest that it is not due to the electrode being in contact with ischemia or infarcted endocardium or only due to loss of local potentials. It also appears that myocardial infarction, per se, may not be directly responsible for the fall in ECP. This is also supported by the clinical observation that transient fall in RVECP may occur in patients undergoing open-heart surgery under deep hypothermia and in some patients with acute massive pulmonary em

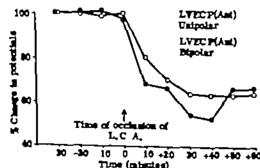


Fig. 4. Changes in simultaneously recorded unipolar (open circles) and bipolar (closed circles) potentials from the anterior wall of the left ventricle before and after ligation of the left circumflex artery.

Table II. Potentials in millivolts immediately before and 60 minutes after ligation of the coronary arteries

Dog No.	Artery occluded	LV ECP (Ant.) (mv)		LV EPP (Ant.) (mv)		LV ECP (Inf.) (mv)		LVEPP (Inf.) (mv)		RVECP (mv)		Lead II	
		Pre*	Post†	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	LAD	30.3	18.4	7.1	5.9	—	—	—	—	23.7	15.2	1.1	1.4
2	LMC	19.1	11.1	10.8	11.7	—	—	—	—	19	14.8	0.4	0.7
3	LCA	34.5	17.0	8.8	7.7	—	—	—	—	11.6	4.0	3	2.0
4	LCA	21.0	17.5	4.7	4.7	10.0	9.5	1.8	19	5.7	5.8	1	1.5
5	LMCA	23.6	11.2	6.8	12.0	9	9.2	10.0	13.0	10.7	11.0	1.4	1
6	LCA	40.6	31.0	20.7	15.2	11.3	6.0	6.8	3	3.0	3.2	1.2	2.0
7	LCA	40.8	27.7	23.0	27.5	4.2	1.6	15.3	13.0	7	3.3	1.2	1
8	LCA	43.0	7.9	19.1	11.0	7.5	3.8	7.3	6.2	—	—	—	—
9	LCA	40.3	26.1	17.9	21.5	20.1	9.6	14.7	7.5	—	—	—	—

*Pre = potentials immediately before coronary artery ligation.
†Post = potentials at 60 minutes after coronary artery ligation.

bolism without previous cardiorespiratory disease.[6]

The postocclusion changes in direct epicardial potential and in potential recorded in Lead II were variable. In most experiments immediately after coronary artery ligation and concurrent with the appearance of the injury pattern, there was some increase in potentials followed by a gradual fall. At 60 minutes, after ligation of the coronary arteries, epicardial potentials were less than the control values in a few animals (Table II). Maxwell, Kennamer, and Prinzmetal[7] also reported abnormally large R waves occurring over the noncontractile muscle during the stage of acute injury after the ligation of the coronary artery. On the other hand, some reduction in voltage of epicardial QRS complex over injured or infarcted myocardium has also been reported by other workers.[8,10] Although in the present study there was usually a slight initial increase in epicardial potential with concomitant fall in endocardial potential after ligation of the coronary arteries, there was later no such consistent reciprocal relationship between simultaneously recorded epicardial and endocardial potentials from either anterior or inferior walls of the left ventricle. For example, in Dog 8 (Table II) there was concomitant fall in both epi- and endocardial potentials recorded from inferior surfaces of the left ventricle (Fig. 1). Thus, persistently low ECP following coronary artery occlusion is unlikely to be due only to cancellation of the potentials at different sites of the ventricle.

Falls of LV dp/dt and aortic pressures following experimental myocardial ischemia or infarction, as observed in this study, have been reported by other workers,[11,12] but the relation between postocclusion changes in LV dp/dt and ECI following coronary artery occlusion has not been previously studied. In general, a fall in LV or RV ECP occurred with marked fall in LV dp/dt and there was a moderate correlation between percentage changes in ECP and changes in LV dp/dt. Pruett and Woods[14] showed significant positive correlation between the amplitude and rate of depolarization of intracellular action potential and myocardial contractile force. In the present study, as preload and afterload not

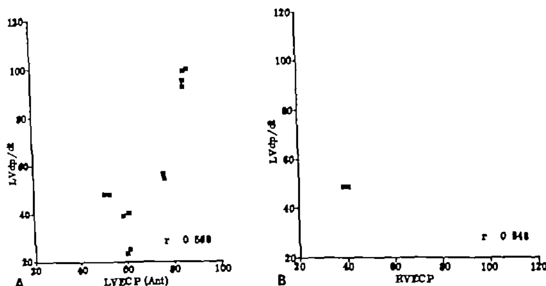


Fig. 5 Relations between percentage changes in the rate of rise of left ventricular pressure pulse (LV dp/dt) and endocardial potential from left ventricular anterior wall (left, = 0.568, P < 0.001) and right ventricular inferior wall (right = 0.548, P < 0.001)

controlled observed changes in LV dp dt cannot be regarded as being representative of true changes in myocardial contractility[13] Hence, although a moderate correlation was found between changes in LV dp/dt and ECP the relationship between myocardial contractility and ECP remain uncertain and further study will be needed for its elucidation

In conclusion it can be said that the present study has demonstrated that falls in ventricular endocardial potentials may occur following acute coronary artery occlusion but the precise mechanism remains obscure. It would seem that localized ischemia or infarction of the myocardium may not be directly responsible for the low ECP Neither does the phenomenon of cancellation of electrical forces at different parts of the ventricles appear to be the cause of persistently low ECP following acute coronary artery occlusion.

The practical importance of the fall in ECP after infarction lies in the use of demand (ventricular inhibited) pacing when needed In demand pacing the signal used to inhibit the pacemaker is the QRS potential When this potential falls below the sensitivity of the pacemaker the unit behaves as a fixed rate apparatus, allowing competition to occur between the patient's own rhythm and the artificial stimulus of the pacemaker Thus inappropriate ventricular stimulation may occur increasing the risk of ventricular fibrillation.[14]

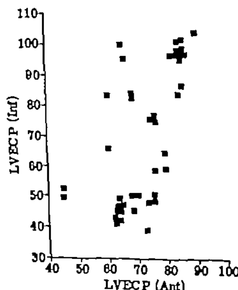


Fig. 6 Relation between endocardial potentials recorded simultaneously from the anterior and inferior walls of the left ventricle following coronary artery occlusion. There was no correlation between LVECP Ant. and LVECP Inf (= 0.128 P > 0.10)



Fig. 7. Two left ventricular endocardial electrodes in a heart examined by injection of dye. Both electrodes were moved at the time of photographs. One electrode was in a nonischemic (dark) area, indicated by the larger arrow, and the other in ischemic areas, indicated by the smaller arrow. Potentials recorded simultaneously from both sites fell following ligation of the left circumflex artery.

Summary

The behavior of right and left ventricular endocardial potentials (ECP) was studied in open-chest anesthetized dogs both before and after ligation of the coronary artery. Endocardial potentials were recorded from the anterior and inferior walls of the left ventricle (LVECP Ant, LVECP Inf) and from the inferior wall of the right ventricle (RVECP). Direct epicardial potentials from the anterior and inferior surfaces of the left ventricle along with ECG Lead II were also recorded. LV dp/dt and aortic pressure were monitored simultaneously. Following ligation of the coronary arteries, LVECP Ant fell in all animals and LVECP Inf and RVECP in most and remained lower than the control values throughout the periods of observation. Fall in ECP occurred whether the endocardial electrodes were in contact with ischemic or nonischemic endocardium. No relationship was found between the postocclusion changes in simultaneously recorded epi and endocardial potentials whether from the anterior or inferior surface of the left ventricle. Neither was any correlation between the changes in endocardial potentials recorded from anterior and inferior surfaces of the left ventricle or between LVECP and RVECP. These findings suggest that the fall in ECP which occurs following acute coronary artery occlusion is unlikely to be due to the phenomenon of cancellation between electrical forces generated at different parts of the ventricle. Neither localized ischemia nor infarction of the myocardium seems directly responsible for the fall in ECP. The precise mechanism remains obscure.

Fall in LV dp/dt and in aortic pressure occurred in most animals following ligation of coronary arteries and there was moderate correlation between postocclusion changes in LV dp/dt and changes in ECP.

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Responses of the ischemic myocardium to allopurinol

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Ischemic myocardium is characterized by a loss of glycogen and potassium and a breakdown of high-energy phosphate compounds in addition to a local release of catecholamines and an accumulation of lactic acid. Metabolic changes occur even in the tissues surrounding ischemic myocardium.[1] The release of inorganic phosphate from hypoxic myocardial cells indicates the breakdown of the high-energy phosphate compounds.[2] Crowell and associates[3] suggested that an irreversible arrest of energy conversion results from the degradation of the high-energy phosphate compounds. Catabolism of these compounds produces the intermediates adenosine, inosine, and other related compounds which diffuse out of the cell ultimately to be converted to uric acid by action of the enzyme xanthine oxidase in the liver. The cell possesses resynthesis pathways so that hypoxanthine and higher compounds can be converted to adenosine triphosphate (ATP); therefore, these compounds are termed functional purine bases. With the conversion of hypoxanthine to xanthine and the conversion of the latter to uric acid by the enzyme xanthine oxidase, the functional purine base becomes irretrievably lost since the conversion of xanthine to uric acid is irreversible. It is known that hypoxic tissues lose purine intermediate compounds to the surrounding fluids but recover and reconvert them if oxygen is restored.[4]

A key to metabolic support of the acutely ischemic myocardium may be the maintenance of the total body pool of functional purine bases by blocking the action of the enzyme xanthine oxidase. These substrates would then be available for reformation of the high-energy nucleotides in the myocardium and the damaged muscle would regain its ability for energy conversion. This would permit recovery of the damaged muscle.

The following experiments attempt to test this hypothesis by evaluating the effect of the xanthine oxidase inhibitor Allopurinol on myocardial function and metabolism following acute myocardial ischemia produced by occlusion of a major coronary artery in open-chest animals.

Methods

Fifty-six experiments were performed on 46 medium-size mongrel dogs and 10 sheep. The animals were quarantined

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treated with anthelmintics, and in the case of dogs immunized against distemper hepatitis, and leptospirosis before being admitted to the study. Halothane anesthesia was used with positive pressure inhalation. The heart was approached through a midline sternotomy incision. The animal's carotid artery, jugular vein and coronary sinus were cannulated for blood sampling after the administration of heparin 500 units per kilogram of body weight. A Statham muscle transducer connected to a Walton-Brodie bridge was sutured in place on the epicardial surface of the left ventricle over the area adjacent to the anterior descending (interventricular) branch of the left coronary artery which was known to become the infarcted area. This provided a measurement of the change in muscle tone. Cardiac output was determined by the dye dilution technique (indocyanine green) using a Gilford densitometer and was calculated by the Stewart Hamilton method. In some of the experiments a Statham electromagnetic blood flow transducer was placed at the aortic root. Femoral artery and central venous pressures were obtained by placing a Teflon catheter into the femoral artery and vein and advancing the latter to the right atrium. Pressures were measured by Statham P23D pressure gauges.

The left anterior descending coronary artery was isolated just distal to the septal branch and a tourniquet placed around it in order to occlude it at will. An occluding tourniquet was also placed around the coronary sinus in order to assure isolated collection of coronary sinus blood. This is of particular importance in sheep because the left azygous (hemiazygous) vein empties into the coronary sinus.

A Lead II electrocardiogram (ECG) was continuously observed and interval recordings were obtained. In all groups the following biochemical measurements were made every 10 minutes for 30 minutes before and for 3 hours after ligation of the coronary artery. After 3 hours the measurements were made less frequently. These measurements were (1) coronary sinus blood uric acid measured by the Keon Stransky Colorimetric Method (2) coronary sinus inorganic phosphorus and (3) coronary sinus potassium. Coronary sinus blood samples were analyzed in duplicate. The variation between duplicate samples was less than 0.1 per cent for uric acid.

The arterial mean blood pressure, cardiac output, and myocardial contractility (gauge) were recorded on a Honeywell visicorder. Allopurinol was used as a parenteral preparation of the sodium salt, in concentrations of 20 mg per milliliter further diluted to 4 mg per milliliter according to the method of Kann and associates.[7]

The following experimental groups were studied.

Control Group I was composed of 10 dogs and 2 sheep in which the anterior descending coronary artery was ligated but no therapy was instituted.

Group II animals 12 dogs and 2 sheep had ligation of the coronary artery followed by the administration of Allopurinol (50 mg per kilogram of body weight) intravenously as soon as ischemic S-T changes were noted in the ECG.

Group III animals, 2 dogs and 12 sheep were pretreated with Allopurinol (50 mg per kilogram of body weight) intravenously prior to ligation of the coronary artery and also received the inhibiting agent during the ischemic period.

Group IV animals, 10 dogs and 6 sheep received Allopurinol intravenously without coronary ligation to evaluate the hemodynamic and biochemical effects of the drug.

Some of the animals in the last group had thoracotomy, in others the chest was not opened. Data were collected at increasing levels of drug infusion i.e. at 50 to 300 mg per kilogram of body weight to determine the toxic levels, if any.

The survival time following ligation was recorded in all animals up to the 8 hour mark. The animals still living were then sacrificed and the heart was serially sectioned at postmortem examination. A statistical analysis of the data was conducted using the paired t test of differences of the means according to Snedecor.

Results

The usual ECG changes including S-T segment depression followed by acute elevation, T wave inversion with progressive

Responses of the ischemic myocardium to allopurinol

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Ischemic myocardium is characterized by a loss of glycogen and potassium and a breakdown of high-energy phosphate compounds in addition to a local release of catecholamines and an accumulation of lactic acid. Metabolic changes occur even in the tissues surrounding ischemic myocardium.[1] The release of inorganic phosphate from hypoxic myocardial cells indicates the breakdown of the high-energy phosphate compounds.[2] Crowell and associates[3] suggested that an irreversible arrest of energy conversion results from the degradation of the high-energy phosphate compounds. Catabolism of these compounds produces the intermediates adenosine, inosine, and other related compounds which diffuse out of the cell ultimately to be converted to uric acid by action of the enzyme xanthine oxidase in the liver. The cell possesses resynthesis pathways so that hypoxanthine and higher compounds can be converted to adenosine triphosphate (ATP); therefore, these compounds are termed functional purine bases. With the conversion of hypoxanthine to xanthine and the conversion of the latter to uric acid by the enzyme xanthine oxidase, the functional purine base becomes irretrievably lost since the conversion of xanthine to uric acid is irreversible. It is known that hypoxic tissues lose purine intermediate compounds to the surrounding fluids but recover and reconvert them if oxygen is restored.[4,5]

A key to metabolic support of the acutely ischemic myocardium may be the maintenance of the total body pool of functional purine bases by blocking the action of the enzyme xanthine oxidase. These substrates would then be available for reformation of the high-energy nucleotides in the myocardium and the damaged muscle would regain its ability for energy conversion. This would permit recovery of the damaged muscle.

The following experiments attempt to test this hypothesis by evaluating the effect of the xanthine oxidase inhibitor Allopurinol on myocardial function and metabolism following acute myocardial ischemia produced by occlusion of a major coronary artery in open-chest animals.

Methods

Fifty-six experiments were performed on 46 medium-size mongrel dogs and 10 sheep. The animals were quarantined

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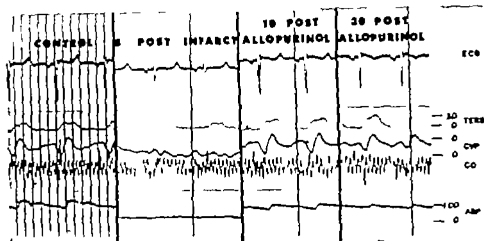


Fig. 2 Example of hemodynamic response t Allopurinol in dog Tracings from top to bottom ECG deflection of Walton-Brodie strain gauge bridge (tension in grams); CVP = central venous pressure CO = cardiac output (mea of aortic flowmeter recording showing 60 cycle interference) ABP = aortic blood pressure. Paper speed = 100 mm. per second. Note impaired contractility (tension) and decreased ABP after ligation of coronary artery and improvement after Allopurinol. CO output showed no significant change in this experiment.

the infarction to levels similar to those of the control group but also returned to normal levels after Allopurinol was administered A summary of the hemodynamic changes in Group II experiments is illustrated in Figs. 3 and 4

Fig 5 illustrates the changes in uric acid and inorganic phosphorus in the coronary sinus samples as a consequence of coronary occlusion and the subsequent administration of Allopurinol. There was a significant increase in coronary sinus uric acid from 0 94 mg per cent to 2 06 mg per cent and inorganic phosphorus from 4 8 mg per cent to 7.0 mg per cent with myocardial ischemia. Following Allopurinol administration in Group II coronary sinus uric acid decreased from the elevated levels after ligation to the preischemia levels of the control group (1 mg per cent versus 0 78 mg per cent) These data represent the changes in the mixed coronary sinus blood and not the changes originating directly from the venous drainage of the infarcted segment. No significant changes were noted in coronary sinus sodium and potassium levels.

About 45 minutes after the Allopurinol injection in a single dose ischemic S-T segment elevation associated with a progressive drop of the blood pressure and left ventricular contractility recurred. A repeat bolus of Allopurinol (1 to 2 Gms.) at this time again improved both the electrophysiologic and hemodynamic parameters. Again no dysrhythmias were noted In two animals (dogs) sudden slowing of the heart rate followed by sinus arrest and complete asystole, occurred between the fifth and sixth hour after coronary ligation The other animals were sacrificed several hours later when no further abnormal trends were noted

Animals pretreated with Allopurinol and which also received repeated injections of the drug (Group III) exhibited a considerable protective effect after left descending coronary artery ligation In the hours following the acute ligation there was a delay of the ECG evidence of infarction i.e. in Q wave changes. Mean blood pressure and cardiac output remained at the control level after a 3 to 5 minute initial drop Pretreatment with the drug appeared to add to the protective effect of postligation infusion of Allopurinol Periodic reinfusions were repeatedly effective. Uric acid and phosphorus levels remained at control levels after coronary artery ligation All animals were sacrificed after seven hours when further hemodynamic changes were not evident.

Administration of Allopurinol in animals without coronary ligation both in those with open thoracotomy and in those intact but anesthetized animals (Group IV) resulted in no significant hemodynamic or biochemical changes. ECG s, arterial blood

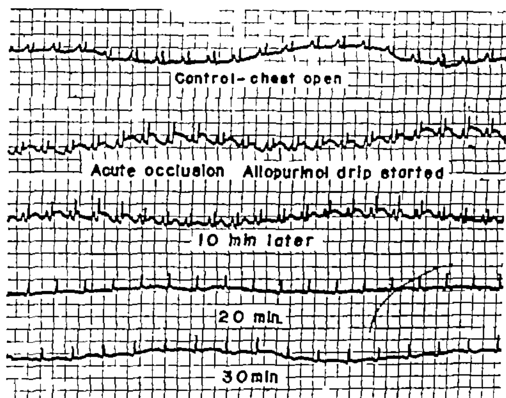


Fig 1 Example of the ECG response of a dog's heart to acute coronary artery ligation followed by intravenous Allopurinol injection, 50 mg per kilogram of body weight, given over a 10 minute period.

Q wave widening and ectopic rhythms (*premature ventricular contraction*) were noted in all experiments within a few seconds after ligation of the left anterior descending coronary artery The ECG changes were accompanied by a well delineated dusky blue area of acute myocardial hypoxia and a decrease in mean arterial blood pressure myocardial contractility and cardiac output In Group I (no treatment) death occurred rapidly in two animals (dogs) due to ventricular fibrillation in spite of attempted resuscitation Animals surviving the acute phase of hypoxia developed an infarction pattern of ECG in the initial 20 to 30 minutes, followed by a gradual decrease in aortic blood pressure (from a mean value of 112 to 82 mm Hg) a decrease in cardiac output from 2 6 to 1 5 L per minute and a 50 per cent decrease in myocardial contractility while the central venous pressure increased from an average of 5 2 to 9 3 mm Hg The contraction of the left ventricle became paradoxical dysrhythmias occurred and the remaining 10 animals died within 2 hours

Intravenous injection of 50 mg per kilogram of body weight of Allopurinol soon after the appearance of ischemic ECG changes (Group II animals) resulted in marked alterations of the expected trends. Within seven minutes, the dusky blue discoloration of the affected heart muscle (due to acute hypoxia) began to return to its normal pink appearance in spite of continued coronary occlusion The ischemic ST T changes instead of progressing to acute infarction with arrhythmias, tended to return toward a basal configuration in all animals without the development of arrhythmias (Fig 1) Fig 2 illustrates the changes of myocardial tension and arterial blood pressure in one of the experiments. Myocardial tension in the infarcted area decreased to 50 per cent of the tension manifested by the controls but returned to control levels or higher after the administering of Allopurinol Aortic and central venous pressures decrease f er

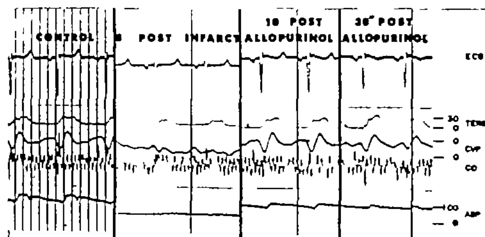


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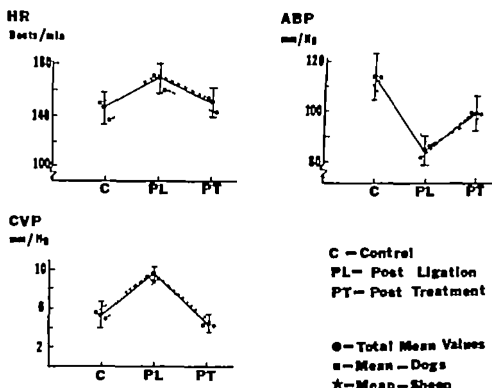


Fig 3 Average changes in heart rate (*HR*) ortic blood pressure (*ABP*) and central venous pressure (*CVP*) before and after ligation of coronary artery and after Allopurinol in Group II animals. Vertical bars are standard errors.

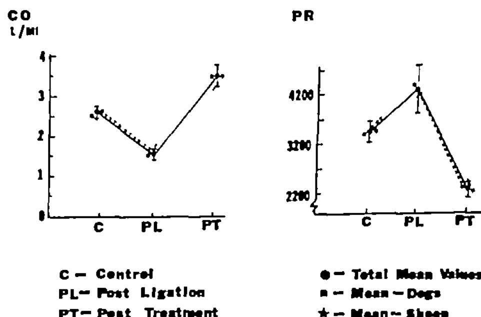


Fig 4 Average hanges in cardiac output (*CO*) and peripheral resi tance (*PR*) before nd after ligation of coronary artery and after Allopurinol i Grou p II a mals. Vertical bars denote standard errors.

pressure central venous pressure blood pH P_{CO_2}, P_{O_2} and base excess were recorded in these animals. No significant changes were observed in periodic right atrial blood samples taken to determine potassium sodium uric acid and inorganic phosphorus levels No alteration in blood P_{O_2} P_{CO_2} or pH were observed No changes occurred in hemodynamics except when levels near 300 mg per kilogram of body weight were reached (Figs. 6 and 7) The cardiac output did not change with lower dosage levels but increased at the highest dosage level When dosage levels of 300 mg

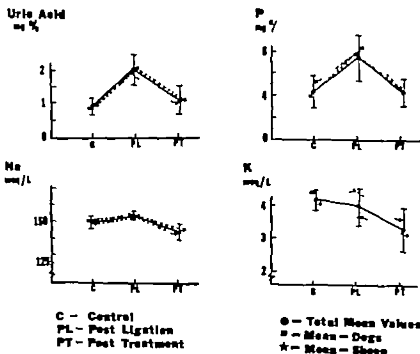


Fig 5 Average changes in uric acid, phosphorus (*P*) sodium (*N*) and potassium (*K*) i the coronary sinus blood in Group II nimals. Changes uric acid and phosphorus were significant t the less than 5 per cent level ($p > 0.05$) after ligation of the coronary artery

per kilogram of body weight were given over a period of 30 to 45 minutes, the blood pressure was significantly reduced. Peripheral resistance decreased 50 per cent severe metabolic acidosis ensued (base deficit −6 to −14) and f uncorrected would have persisted however the animals remained alive even in the face of the profound hemodynamic change The hemodynamic changes which began to manifest themselves around the level of 100 mg per kilogram of body weight reached significance only at the level of 300 mg per kilogram of body weight ($p < 0.05$)

Discussion

The experiments have shown that Allopurinol had a considerable protective effect on the ischemic deterioration of myocardial function. It prevented the usual hemodynamic consequences of d minished myocardial contractility and the development of dysrhythmias follow ng coronary artery ligation Concomitantly it appeared to have a reversing effect on the disturbed purine metabolism of the ischemic heart, as concluded from the changes in the coronary sinus metabolites. There was no significant difference in the results for dogs and sheep While we have shown the average changes in the two species separately we felt that averaging the changes in all animals studied was also justified

In the untreated animals ECG changes occurred during the first few seconds after coronary artery ligation which results are in agreement with the findings of Olsson and Gregg and other investigators. These changes were notably the development of a deep Q wave the widening and notching of the QRS complex, moderate to severe S-T segment changes, and occasional ectopic beats. The ECG change was accompanied by the development of the typical dusky blush infarct area

In our control group of animals during the evolution of the infarction there was first a sudden decrease of the arterial blood pressure and myocardial contractility accompanied by an increase in central venous pressure. These parameters seemed to improve temporarily and after 20 to 30 minutes a gradual but steady decrease in arterial blood pressure, in cardiac output, and in

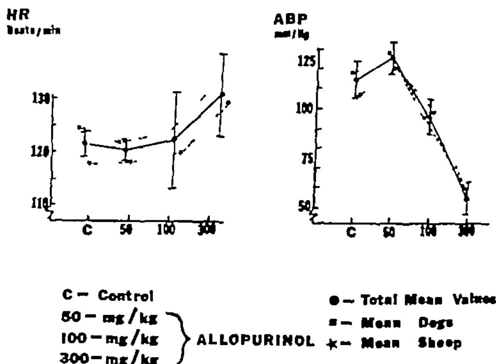


Fig. 6. Average heart rate (*HR*) and aortic blood pressure changes (*ABP*) in Group IV animals at different dosages of Allopurinol.

contractility developed along with a corresponding rise in central venous pressure. This temporary improvement may be due to a temporary boost of anoxic tissue metabolism from an unknown cause. The coronary sinus uric acid and phosphorus levels began to rise immediately after ligation.

The mechanism of the protective effect of Allopurinol is not known and we can only speculate on its operation. It is known that Allopurinol is a competitive inhibitor of xanthine oxidase which is converted in all living animals to oxypurinol. In man, Allopurinol is cleared rapidly but oxypurinol appears to be reabsorbed by the kidney tubule and is excreted slowly. Oxypurinol is in itself an inhibitor of the enzyme xanthine oxidase.[9] A small amount of xanthine oxidase exists in heart tissue.[10] Uric acid is considered as the end product of the action of the xanthine oxidase on hypoxanthine and xanthine. These are being formed in turn by the deamination of the adenine and guanine of the nucleic acids. When the action of xanthine oxidase is inhibited, the oxypurines are protected from catabolic destruction and a considerable degree of reutilization may occur in the anabolism of nucleic acid adenine and guanine.[11] Thus, by maintaining a high pool of purine base within the body, these substances may be available by mass action for reutilization of depleted stores, rather than being converted to the end product, uric acid. Thus they may have an important protective effect on ischemic myocardial metabolism. It is reasonable to speculate that the increasing coronary sinus uric acid after coronary ligation in the untreated animals came from the purine base lost from the hypoxic myocardial cell and that the increased coronary sinus inorganic phosphorus came from catabolism of the high energy phosphates from these same hypoxic cells. Allopurinol seemed to reverse this process.

The pinking of the ischemic area following the use of Allopurinol would seem to indicate that there exists some neural or humoral effect of the agent resulting in the opening of previously nonfunctioning intramural channels or collaterals or in the prevention of vasospasm, resulting in a chemical revascularization of the myocardium. This mechanism will have to be studied further. It seems reasonable, however, to postulate that the preservation of the metabolic pool of nucleotides and the accumulation of intermediary products such as adenosine compounds, especially cyclic ATP, may result in a general vasodilatory effect which would overcome the coronary vasospasm as described by Gray

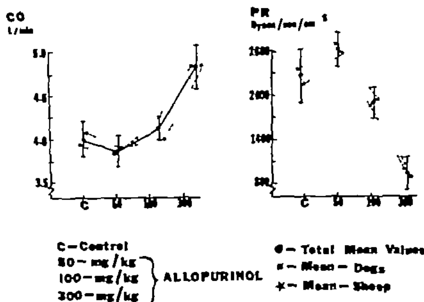


Fig. 7. Average cardiac output (*CO*) and peripheral resistance (*PR*) in Group IV animals at different dosages of Allopurinol. Changes were significant at the less than 5 per cent level ($p < 0.05$) only for the dosage 300 mg. per kilogram of body weight.

son and colleagues[12,13] and by Berne and associates.[14,15]

The antiarrhythmic effect of Allopurinol may also be related to this or to an electrochemical phenomenon resulting from prevention of potassium loss from the myocardial cell. This may have an electrical stabilizing effect. However, no change in coronary sinus potassium has been shown in our experiments. This may be due to dilution in the mixed coronary sinus blood sample not reflecting small local potassium changes. The importance of this ion in the development of dysrhythmia leading to fibrillation was well documented by Regan and colleagues. Logic and colleagues[17] have suggested that halothane possibly has an antiarrhythmic effect by acting at the Phase IV depolarization site. Although it could be argued that this was contributory to the prevention of arrhythmia noted in this study, there was no effect on the development of arrhythmia in the control group. Therefore, we must conclude that if halothane had such an effect, it was negligible in those experiments.

Summary

Allopurinol was found to have a profound effect on hemodynamic, ECG, and biochemical changes of experimental myocardial ischemia produced by coronary artery ligation in dogs and sheep. Following acute infarction, intravenously administered Allopurinol caused an increase of myocardial contractility and cardiac output, reversed or prevented electrocardiographic S-T changes of ischemic origin, and exhibited prolonged antiarrhythmic effects. It is suggested that prevention of the irreversible loss of purine base from the cell during hypoxic states is the biochemical action of this drug that results in rapid recovery of the stressed myocardium. The results of the experiments indicated that Allopurinol may be a useful agent for the treatment of coronary insufficiency.

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Body composition in mitral cachexia

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Wasting may be a prominent symptom of chronic mitral stenosis and can occur in the absence of evident edema. Previous studies have demonstrated that total exchangeable sodium and extracellular water are increased in patients with severe mitral disease and congestive heart failure[1-4] and in dogs with spontaneous heart failure. A few investigators have described a decrease in total exchangeable potassium and intracellular water in such patients.[4] However, we are not aware of any studies of body composition that describe in detail the nature of the cachetic state.

Methods and calculations

Mitral stenosis was produced in five adult mongrel dogs as a part of a larger study on the pathogenesis of pulmonary vascular occlusive disease (Hawe, A., et al. Unpublished data). A detailed description of the operative procedure is presented elsewhere. Briefly, Teflon cloth-covered metal rings with orifices of various sizes were sutured into the mitral annuli of the animals during cardiopulmonary bypass in such a manner as to leave the mitral leaflets intact and thus preserve the competence of the valve. The mitral valve was exposed through an incision in the anterior wall of the left atrial appendage, well removed from the left atrial pulmonary venous junction.

The rings were constructed of stainless steel 0.06 inch thick and covered with the Teflon cloth in such a manner as to leave an outer margin for the placement of sutures. The external diameter of the metal ring varied between 2 and 3 cm. Gorlin's formula[7] for resistance across the mitral valve was used to calculate the ring orifice size required to raise the mean left atrial pressure to approximately the desired level in each animal. Central or peripheral left-to-right shunts were made in three animals one month prior to the insertion of the mitral occlusive ring. Bilateral shunts between the femoral artery and vein were made in two dogs (Nos. 2 and 3), and a central shunt was made between the main

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Table I Total body fluids electrolytes and body composition in experimental mitral cachexia in dogs

Dog	Weight (Kg)		Exchangeable sodium (Na)		Exchangeable potassium (K)		Ratio of Na to K	(K)i (mEq/L)
	Initial	Final	mEq	mEq/Kg	mEq	mEq/Kg		
Experimental								
1	23 5	17 5	1 025	58 57	971	55 48	1 06	154 2
2	22 8	18 0	1 277	70 94	1 176	65 33	1 08	172 5
3	19 0	15 0	88[illegible]	58 80	918	61 20	0 96	160 8
4	20 0	16 4	967	58 96	857	53 56	1 12	155 3
5	22 0	16 2	804	49 62	826	50 98	0 97	144 2
Mean	21 5	16 6	991	59 67	949	57 33	1 04†	157 4
S D	—	1 2	181	7 59	138	5 84	0 07	10 4
Control								
1		17 4	893	51 32	1 107	63 62	0 81	158 8
2		19 9	818	45 70	885	49 44	0 92	164 4
3		15 2	717	47 17	835	54 93	0 85	164 4
4		15 9	764	48 05	881	55 40	0 86	158 8
5		16 1	710	44 10	804	49 94	0 88	152 6
Mean		16 5	780	47 26	902	54 66	0 86	159 8
S.D		1 1	88	2 71	119	5 70	0 04	4 9

*Significant difference from control, $p < 0.05$.
†$p < 0.01$

pulmonary artery and ascending aorta in one dog (No 5) (Table I) In these three animals the size of the orifice of the mitral occlusive ring depended on the increment in pulmonary blood flow achieved by the shunt and was again calculated with the use of Gorlin s formula to raise the mean left atrial pressure to approximately the same level as in the two dogs with mitral stenosis alone (Nos 1 and 4) Subsequent hemodynamic studies demonstrated a mean diastolic gradient of 21 3 cm water (S E 5 3) across the mitral valve Left atrial hypertension and pulmonary artery hypertension were also present Video angiocardiography showed dilatation of the left atrium

After surgery all animals received 600 000 U of penicillin and 1 Gm of streptomycin daily for 7 days. Anticoagulation was accomplished with 2 5 mg of sodium warfarin each day throughout the postoperative period

Two dogs with experimental mitral stenosis as the only lesion and one dog with mitral stenosis and bilateral peripheral arteriovenous fistulas were killed after completion of all studies. At autopsy the left atria were enlarged but free of thrombi, and the occlusive rings were well encapsulated by host tissue The left atrial walls were hypertrophied with areas of fibrosis and calcification in the endothelium.

Fifteen to 23 months after the operation a battery of chemical determinations were performed on blood obtained from the experimental group and from five control dogs matched for weight Studies of total body fluids and electrolytes and body compartmentalization were carried out on both groups.

Plasma volume was determined with the use of Evans blue After the intravenous administration of 5 ml blood samples were drawn at 15 30 and 45 minutes for colorimetric analysis of Evans blue concentration in the plasma. The volume of distribution was obtained by use of reverse extrapolation to zero time.

Simultaneous determinations of total body water exchangeable sodium and exchangeable potassium were performed

Ten milliliters of deuterium oxide (99 8 per cent) and 5 ml of 0 85 per cent NaCl containing 25 to 50 μc of ^{24}Na and 50 to 100 μc of ^{42}K were injected simulta[illegible]

Table II Total body fluids electrolytes and body composition in experimental mitral cachexia in dogs

Dog	Total body water		Extracellular water		Intracellular water		Plasma volume		Lean body mass		Fat	
	L	%	L	%	L	%	L	%	Kg	%	Kg	%
Experimental												
1	11.84	67.6	5 79	33 1	6.05	34 6	0.99	5 7	15.85	90 6	1.65	9 4
2	13.06	72.6	6.43	35 7	6.63	36.8	1 19	6.6	17 49	97.2	0.51	2.8
3	10.90	72.7	5.36	35 7	5.57	36.9	—	—	14.59	97.3	0.41	2.7
4	10.33	63.0	5.05	30.7	5.28	32.2	0.93	5.8	13.82	84.3	2.58	15 7
5	10.39	64 1	4.82	29.8	5.57	34 4	1 10	6.8	13.91	85 9	2.29	14 1
Mean	11.30	68.0	5 49*	33.2	5.81	35 1	1.05	6.2	15.13†	91.0†	1 49†	9.0†
S.D	1 15	4.6	0.64	2.6	0.53	1.7	0.11	0.6	1.54	6.1	0 99	6.1
Control												
1	12.15	69.8	5.32	30.6	6.83	39.2	—	—	16.27	93.5	1 15	6.5
2	9.84	55 0	4 40	24.6	5 44	30 4	—	—	13 17	73.6	4 73	26 4
3	9 08	50 7	4.12	23.0	4 96	32.6	—	—	12.16	80.0	3.04	20.0
4	10.12	56.5	4 72	26.4	5 40	34.0	—	—	13.53	85.2	2.35	14.8
5	9 17	57.0	4.04	25 1	5 13	31 9	—	—	12.28	76.3	3.82	23 7
Mean	10.07	57.8	4.52	25 9	5.55	33.62	—	4.80‡	13 49	81 7	3.01	18.3
S.D	1.23	7 1	0.50	2.9	0.73	4.35	—	—	1.66	7.9	1.38	7.9

*Significant difference from control, $p < 0.025$.
†[illegible] 0.01.
‡Data from [illegible] and Conn.

Urine was collected at 4 and 6 hours and aliquots were analyzed in duplicate by mass spectrometry for the ratio of heavy hydrogen to natural hydrogen according to the method proposed by Solomon, Edelman and Soloway[11] Urine collection was continued for 24 hours to achieve equilibration of radioisotopes and to account for the urinary losses. Spot urine was collected within the next few hours, and a blood sample was drawn at the same time. Specific activities were calculated according to standard formulas.

The calculations of sodium space representing extracellular fluid volume and those of exchangeable sodium and exchangeable potassium were carried out by the use of radioisotopes ^{24}Na and ^{42}K, according to methods previously described

The derived value of intracellular water was obtained by subtraction of extracellular water from total body water Intracellular potassium concentration was calculated by subtraction of extracellular potassium from total exchangeable potassium. This value was then divided by the value for intracellular water to give the concentration of potassium in intracellular water

Total body fat was calculated according to the formula proposed by Pace and Rathbun which assumes that body fat is anhydrous and that the fat-free body has 73.2 per cent water Lean body mass was obtained by subtraction of total body fat from body weight.

Results

Serum or blood analyses for sodium potassium chloride, pH CO_2 content, calcium magnesium total protein albumin globulin urea, creatinine sugar thyroxine, and osmolal concentrations revealed no abnormalities in either the experimental or the control groups.

The results of the studies on total body fluids and electrolytes and body composition are summarized in Tables I and II

The experimental group had an average weight loss of 4.84 kilograms or 23 per cent of the initial weight. The value for exchangeable sodium of 59 67 mEq per kilogram noted in the experimental group was significantly higher ($p < 0.05$) than the value of 47.26 mEq per kilogram noted for control dogs of the same weight. Although the value for exchangeable potassium was

Table III. Comparison of probable initial values with observed values in experimental mitral cachexia in dogs

	Probable initial value*	Observed value†	Change	% change
Weight (Kg.)	21.46	16.62	−4.84	−23
Exchangeable sodium (mEq.)	1,014	991	−23	−2
Exchangeable potassium (mEq.)	1,173	949	−224	−19
Total body water (L.)	12.84	11.30	−1.54	−12
Extracellular water (L.)	5.56	5.49	−0.07	−1
Intracellular water (L.)	7.21	5.81	−1.40	−20
Plasma volume (L.)	1.03	1.05	+0.02	+2
Lean body mass (Kg.)	17.53	15.13	−2.40	−14
Fat (Kg.)	3.92	1.49	−2.43	−62

*Values calculated by the use of the original weight of the dog multiplied by the average normal value of the parameter.
†Values determined 15 to 23 months after operation.

comparable in the two groups, the ratio of exchangeable sodium to exchangeable potassium of 1.04 for the stenotic dogs was higher than the value of 0.86 observed for controls ($p < 0.01$). The concentration of potassium in intracellular water of the two groups was similar. The stenotic dogs had no decrease in intracellular potassium concentration. Although the total body water was 1.23 L. greater in the stenotic dogs than in controls, the difference was not significant. The mean extracellular value of 5.49 L. of the experimental group was significantly higher than the mean of the controls (4.52 L.). The value for intracellular water of the two groups was not different. The lean body mass of the experimental dogs constituted 91 per cent of the total weight, a value significantly higher ($p < 0.05$) than the value of 81.7 per cent for the control dogs. These differences were reflected in total body fat, where the control dogs had 3.01 kilograms of fat and the stenotic group had less than half this amount (1.49 kilograms). These differences were statistically significant ($p < 0.05$).

Discussion

Interpretation of the experimental data presents a dilemma. If the body composition of the stenotic dogs was compared to that of the weight-matched control dogs, comparable amounts of exchangeable potassium and intracellular water were present. The values for exchangeable sodium, extracellular water, plasma volume, and lean body mass were increased and that for fat was decreased, suggesting that fat was lost and replaced by extracellular fluid. The high ratio of exchangeable sodium to exchangeable potassium seems to be due to a relatively high content of exchangeable sodium. However, an alternative interpretation is probably more realistic. Although the body composition of the experimental group was not determined prior to surgery, a reasonable estimate can be made by multiplying the original weight of the dogs by the average normal values of the various parameters studied. Table III summarizes these calculations. The probable initial body composition (column 1) was compared to the actual values determined 15 to 23 months later (column 2). When this was done, the values for exchangeable sodium, extracellular water, and plasma volume did not change. However, a marked decrease in exchangeable potassium, intracellular water, total body weight, lean body mass, and fat occurred. Intracellular water decreased 20 per cent, lean body mass decreased 14 per cent, and fat decreased 62 per cent. The decreases in exchangeable potassium, total body weight, and lean body mass were due entirely to loss of cellular tissue, and the high ratio of exchangeable sodium to exchangeable potassium was the result of a diminished value for exchangeable potassium and could not be attributed to an increase in exchangeable sodium value. The concentration of potassium in intracellular water remained

normal. The dogs lost an average of 4.84 kilograms of weight, of which half was fat and half was lean body mass. Thus the dogs protected but did not increase their plasma volume and extracellular space having lost protoplasm and fat as a result of the cachetic process.

Examination of the experimental dogs at the time of this study, 15 to 23 months after surgical production of mitral stenosis, disclosed no suggestion of peripheral or pulmonary edema. All dogs were emaciated although only one appeared to be weak. The cause for the marked weight loss was not evident. All dogs ate well and seemed to be constantly hungry. Although the exact caloric intake was not determined, all observers agreed that the dogs ate more than other dogs of comparable weight and each received a daily food supplement. The stools appeared to be normal. Metabolic balance studies were not attempted because we believed it unlikely such studies could yield useful information. For example, we estimated that the stenotic dogs lost approximately 225 mEq. of potassium during an average period of about 500 days. The net loss of 0.5 mEq. of potassium each day could not be detected by balance techniques. The dogs also had a large caloric deficit as a result of the wasting process. We have estimated that these dogs lost an average of 2.4 kilograms of fat and 2.4 kilograms of protoplasm (protein and water). This represented a loss of potential energy of 22,548 calories.* On the assumption that weight was lost evenly over the entire postoperative period, the average daily caloric deficit was approximately 45 calories per day or 2 calories per kilogram per day—a value that could not be detected by balance techniques. Two dogs (Nos. 2 and 3) had virtual depletion of their stores of body fat but had lost relatively little protoplasm (lean body mass). Another (No. 5) however appeared to have lost relatively more protoplasm and less fat and appeared to be the weakest and most cachetic of the group. It is worth noting that a net caloric deficit of 1,000 calories requires the expenditure of only 120 grams of body fat, whereas if protein is used as fuel, 1,000 grams of protoplasm will be lost. It is obvious that inanition would eventually cause the death of these animals even if cardiac failure did not supervene.

Intracellular potassium concentration remained normal despite the wasting process, a finding in variance with others who noted a decrease in cellular potassium concentration in man and animals with heart failure. The absence of heart failure in the dogs in our series may account for these differences. The low values of intracellular potassium in heart failure may be due, therefore, to increased hydration of the cell rather than a decrease in the potassium to nitrogen (protein) ratio of cellular tissue. This suggestion has been made by others.

Because of the excellent appetite of the dogs in our series and the absence of an obvious route for caloric wastage, the daily net caloric deficit probably can be attributed to an increased caloric requirement. It has been suggested that humans with severe heart disease are hypermetabolic, although the etiology of the hypermetabolic state is unknown. Our studies provide no data on this point.

Whatever the cause of the cachetic state that occurs in dogs with chronic mitral stenosis, it is obviously of a magnitude that is of clinical significance. Dogs with such stenosis become cachetic and lose fat and protoplasm without clinical or chemical evidence of an absolute expansion of either the plasma volume or extracellular water. Clarification of the etiology of this debilitating circumstance must precede rational efforts to prevent its occurrence in patients with chronic heart disease.

*Calorie = 2,400 (0.[illegible] × 9.3 + 2,400 (0.25 × 4.1, in which 0.[illegible] and 0.25 are the lipid and protein content of body fat and body protoplasm, respectively, and 9.3 and 4.1 are values for the caloric content of 1 Gm. of fat and protein, respectively.

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Table III Comparison of probable initial values with observed values in experimental mitral cachexia in dogs

	Probable initial value	*Observed value†*	*Change*	*% change*
Weight (kg)	21 46	16 6	−4 84	−23
Exchangeable sodium (mEq)	1 014	991	−23	−2
Exchangeable potassium (mEq)	1 173	949	−2 4	−19
Total body water (L)	12 84	11 30	−1 54	−12
Extracellular water (L)	5 56	5 49	−0 07	−1
Intracellular water (L)	7 21	5 81	−1 40	−20
Plasma volume (L)	1 03	1 05	+0 0[illegible]	+2
Lean body mass (kg)	17 53	15 13	− 40	−14
Fat (kg)	3 92	1 49	−2 43	−6[illegible]

*Value calculated by the use of the original weight of the dog multiplied by the average normal value of the parameter
†Value determined 15 to 23 months after operation.

comparable in the two groups the ratio of exchangeable sodium to exchangeable potassium of 1 04 for the stenotic dogs was higher than the value of 0 86 observed for controls (p < 0 01) The concentration of potassium in intracellular water of the two groups was similar The stenotic dogs had no decrease in intracellular potassium concentration Although the total body water was 1 23 L greater in the stenotic dogs than in controls the difference was not significant The mean extracellular value of 5 49 L. of the experimental group was significantly higher than the mean of the controls (4 52 L.) The value for intracellular water of the two groups was not different The lean body mass of the experimental dogs constituted 91 per cent of the total weight a value significantly higher (p < 0 05) than the value of 81 7 per cent for the control dogs. These differences were reflected in total body fat where the control dogs had 3 01 kilograms of fat and the stenotic group had less than half this amount (1 49 kilograms) These differences were statistically significant (p < 0 05)

Discussion

Interpretation of the experimental data presents a dilemma If the body composition of the stenotic dogs was compared to that of the weight matched control dogs, comparable amounts of exchangeable potassium and intracellular water were present The values for exchangeable sodium extracellular water plasma volume and lean body mass were increased and that for fat was decreased suggesting that fat was lost and replaced by extracellular fluid The high ratio of exchangeable sodium to exchangeable potassium seems to be due to a relatively high content of exchangeable sodium However an alternative interpretation is probably more realistic. Although the body composition of the experimental group was not determined prior to surgery a reasonable estimate can be made by multiplying the original weight of the dogs by the average normal values of the various parameters studied Table III summarizes these calculations The probable initial body composition (column 1) was compared to the actual values determined 15 to 23 months later (column 2) When this was done the values for exchangeable sodium extracellular water and plasma volume did not change However a marked decrease in exchangeable potassium intracellular water total body weight lean body mass, and fat occurred Intracellular water decreased 20 per cent lean body mass decreased 14 per cent and fat decreased 62 per cent The decreases in exchangeable potassium total body weight and lean body mass were due entirely to loss of cellular tissue and the high ratio of exchangeable sodium to exchangeable potassium was the result of a diminished value for exchangeable potassium and could not be attributed to an increase in exchangeable sodium value The concentration of potassium in intracellular water ... and

Case reports

Wenckebach phenomenon in the posterior division of the left branch

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In the last few years frequent reports have been published of several cases of complete right bundle branch block (CRBBB) combined with block in the an terior (or superior) division of the left bundle branch (left anterior hemiblock) More recently some cases of block in the posterior (or inferior) div sion of the left bundle branch (left posterior hemiblock) either isolated[2] n or combined with CRBBB[3,4] have also been described In addition reports have been published referring to cases of a new electrocar diographic pattern characterized by CRBBB combined with left anterior hemi block(LAH) plus left posterior hemiblock (LPH) the so-called intraventricular trifascicular block.

In the present report another example is described of an intraventricular tri fascicular block, which reveals certain particular aspects h therto not described namely a conduction defect n the pos terior division of the left branch showing a Wenckebach phenomenon

Case report

H. F N 56-year-old man, presented from 1964 to 1967 several electrocardiograms (ECG') showing typical complete left bundle branch block (Fig. 1) I 1967 he began to complain of dizziness. On July 8, 1968 he wa admitted to the hospital ith Adams-Stokes ttacks During his tay t the hospital he did not mention cardiac pain, nd serial serum enzyme tudies failed t reveal abnormal values Various ECG repe tedly showed simila pattern (Fig. 2) an trial rat between 71 nd 88 beat per minut 2 1 A-V block, P R intervals of the conducted beats measuring 0.32 second, QRS duration of 0.16 second, a typical pattern of CRBBB revealed in the precordial leads, and marked left axis deviation (−70°) in the limb leads The tracings were interpreted indicating 2 1 A-V block nd combined CRBBB and LAH.

On Aug. 7 1968 a final ECG (Fig. 3) showed an pparently complex arrhythmia. Certain aspects of the previous ECG' that had been taken were maintained, i.e., 2 1 A V block with P R prolongation and CRBBB pattern in the precordial leads. On the other hand, the QRS of the limb leads, simultaneously recorded ith the precordial ones, exhibited highly variable feature from beat t be t. It was possible to distinguish tw extreme patterns, which e shall call types A and B (Fig. 4) Type A displayed P R interval measuring 0.28 second nd maintained the pattern of LAH ($\hat{A}_{QRS}$ = −60°) Type B showed P R interval 0 03 to 0.04 second longer than that of type A and completely opposit $\hat{A}_{QRS}$ (+110°) As there ere no other causes for right axis deviation, the pattern was interpreted as meaning CRBBB plus LPH. I the sequence of the strips all the intermediate features between these two extreme morphologies could be seen (Figs. 3 nd 5) However while the transition from type B to A was always sudden, the change from type A to B was most often gradual sometimes when observing the transitional variation from type A to B it was possible to note that the hange was more

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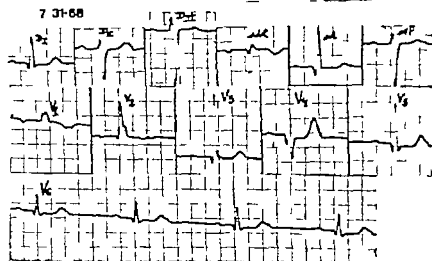


Fig 2 2 1 A V block ith CRBBB + 1 AH (July 31 1968)

reveal this phenomenon within the bundle branches when the ventricular conduction system was converted into a monofascic ular system. They obtained such results after sectioning one branch and just slightly damaging the other Moreover several authors have recently described very sug gestive features in clinical examples of the Wenckebach phenomenon in the left bun dle branch block[4] or in bilateral bundle branch block.

Since the description of the so-called hemiblocks is very recent there have been h therto no references to a Wenckebach phenomenon in this type of block. More over the emphasized nfrequency of the LPH is likely to be another explanation for the occurrence of this feature in the ECG being so rare However it does exist as the present description clearly indicates.

This case represents one of nature s re markable experiments. Beside being fu ther proof of the trifascicular behavior of the intraventricular conduction sys tem t presents a clear-cut demonstra tion that the Wenckebach phenomenon may a tu lly occu in any one of the two divisions of the left bundl branches, that is to say in the posterior one too just as n any other segment of the conduction system subject to partial impairment of conduction. In addition the occurrence in this tracing of a pattern of CRBBB + LAH alternating w th CRBBB + LPH w thout evidence of myocardial infarction, gives information regarding initial ven tricular activation in patients w th left hemiblocks. In the former the initial ven tricular activation is achieved only via the posterior division in the latter it de pends merely on the anterior division The deta led study of the orientation of forces of the first m lliseconds in the ECG s and in the VCG s of this case allows a careful analysis of the very recently re-evaluated problem concerning early left ventricular activation. In this respect the present case furnishes even more information than those two reported by Castellanos and colleagues in which "changes in the chest leads are more difficult to analyze due to the presence of acute septal infarc tion a process which by itself can re orient to initial vectors." However these aspects and their clinical mplications in the ECG diagnosis have been presented elsewhere.

Summary

During several weeks time the ECG s of a patient showed a Mobitz type 2 A V block and a combined CRBBB and marked left axis deviation (LAH) Finally a record was obtained exhibit ng CRBBB combined with either LAH or LPH This last tracing was interpreted as an example of the occurrence of an intraventricular trifascicular block. The patient died four days later in cardiac arrest

The peculiar pattern of transition from

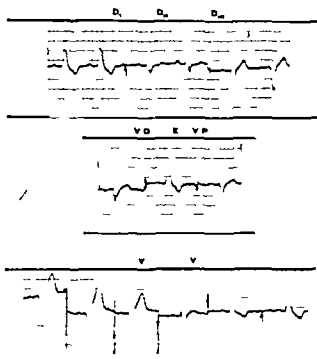


Fig. 1. CLBBB with a P-R interval of 0.22 second (May 20, 1964).

rapid in the first QRS complexes of the cycle than in the last ones (Fig. 5).

Four days later the patient died in cardiac arrest. Postmortem examination was not performed.

Discussion

The last tracing showing a CRBBB combined with LAH alternating with LPH was interpreted as an example of intraventricular trifascicular block.[2,8] However, certain features justify a brief comment.

It is obvious that the block in the anterior division of the left branch was not complete. Otherwise an additional block in the posterior division either would have originated a pattern of complete A-V block or would have preserved the CRBBB plus LAH pattern combined with a further prolongation of the P-R interval. We may assume that the incomplete LAH was probably fixed since the QRS morphology did not change throughout the several tracings obtained after admission.[2] In that case, the difference between the duration of the P-R interval in type B and that in type A, viz., 0.03 to 0.04 second, should indicate the delay of the stimulus in the anterior division which becomes apparent when it can no longer travel through the posterior division.[4]

The most curious aspect of the tracing is the pattern of transition between the two extreme types. This is particularly apparent in Leads D_2 and aV_F (Fig. 3) and Lead D_3 (Fig. 5). A progressive and cyclic change from type A (LAH) to type B (LPH) and a sudden shift from type B to A is seen. If we accept that the LAH is fixed, the referred to aspect points out a progressive and cyclic block in the posterior division until a maximum is attained with no conduction at all through this pathway (LPH) immediately followed by a QRS complex indicating that the conduction was again restored through this division (LAH) with repetition of the cycle. In other words, this aspect clearly *suggests a Wenckebach phenomenon in* the conduction defect of the posterior division. This interpretation is further supported by the finding that the transition is more rapid in the first complexes of the cycle than in the last ones, as happens in the Wenckebach phenomenon commonly found above the bifurcation of the His bundle.

It is possible to go further in the analysis of the conduction defect of the tracing. If we accept that the delay in the anterior division was 0.03 to 0.04 second and that a delay of 0.02 second in one of the two divisions of the left bundle branch causes all the activation of the left ventricle to be achieved through the other division,[4] then we can put forward the following assumptions. If the delay in the posterior division is 0.02 second or less, the QRS will assume the pattern of LAH (A type). When the delay is 0.06 second or more, the QRS will assume that of LPH (B type). Between those two limits the stimulus will activate the left ventricle through both divisions. Fusion beats will result: the longer the delay in the posterior division, the closer to type B will be the pattern of QRS and vice versa.

Although the Wenckebach phenomenon is very common above the bifurcation of the His bundle, it is not easily detected below the bifurcation. Several authors, quoted by Rosenbaum and associates,[10] pointed out that such a phenomenon was never observed in that location. However, Scherf and Shookhoff[11] presented experimental evidence that it was possible to

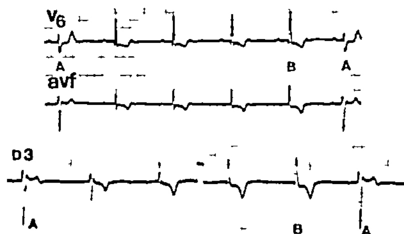


Fig. 5 Same record as in Figs. 3 and 4 The two strips show progressive change from A t B type of the QRS complex and sudden shift from B to A type: it can be observed that the change i the morphology is more marked in the first complexes of the cycle and is slighter in the last ones.

LAH to LPH is discussed and it is concluded that it clearly points to a Wenckebach phenomenon in the posterior division of the bundle branch a conduction defect not hitherto described

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Fig 3 Last record Aug. 7 1968 (see text for explanation)

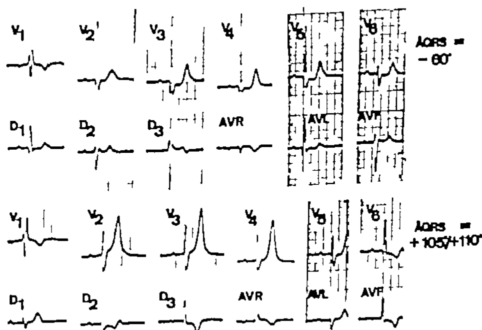


Fig 4 Same record as in Fig 3 In the top two rows, the 12 lead ECG corresponding to A type; in the bottom two rows, the ECG corresponding to B type (see text for explanation)

Angiocardiographic tudy of the right-sided pul monary (anatomic left) ventricle revealed hypoplastic chamber ith no direct connection t either the great vessels or the other ventricle Dilated myocardial sinusoid i the wall of this mall cavity ere opacified. These retrogradely filled the coronary arterial system and fai tly opacified the ascending aorta (Fig. 4 A nd B) These tudies ere interpreted showing corrected transposition of the great vessels ith pulmonary tresia, intact ventricular septum, and hypoplasia of the blood right-sided pulmonary (anatomic left) ventricle The catheterization data are included in Table I

T day following cardiac catheterization, right-sided subclavian artery pulmonary artery anastomosis was performed. Following this procedure, the infant showed initial improvement On the sixth postoperativ day cyanosis uddenly became more intense, nd the baby became more irritable Before trial septostomy or second systemic pulmonary shunt could be ttempted, cardiac arrest occurred, and the patient could not be revived.

Pathology

The heart was noted to be markedly enlarged weighing 50 grams and consisting predominantly of the left-sided ventricle. The aorta arose anteriorly and to the left of the pulmonary artery (Fig 5). Both tria ppeared dilated. A patent foramen ovale was noted hich measured 0.8 cm. in diameter A 0.3 cm. secundum trial septal defect wa also present. The right-sided trioventricular alve was bicuspid nd markedly hypopla tic the annulus measured 0 6 cm. in circumference. The small cavity of the right-sided ventricle was lined by thick hite endocardium.

The myocardium was hypertrophied measuring 1 4 cm. in thickness. N pulmonary outlet from this chamber was present and the ventricular sept m was intact. Small sinusoidal openings ere visible within the ventricular myocardium.

The 4 pulmonary veins entered an enlarged left trium in the normal fashion. The left trioventricular valve was tricuspid and the annulus markedly dilated, measuring 6 0 cm. in circumference. The septal cusp was adherent to the septal wall, and crista-supraventricularis separated the medial cusp from the aortic valve (tricuspid-aortic discontinuity) The endocardial surface was coarsely trabeculated, characteristic of an anatomic right ventricle. The chamber was grossly dilated, but the myocardium was only slightly hypertrophied, measuring 0 7 cm in thickness.

The ascending aorta was large and the coronary arteries ere transposed. The right coronary artery arose from the nterior aortic sinus and gave rise to the anterior descending coronary artery as is usually the case in corrected transposition of the great vessels. The left coronary artery originated from the posterior coronary sinus and descended in the posterior interventricular groove. The pulmonary artery was posterior and had circumference pproximately one third that of the aorta. The pulmonary orifice was tretic and no valve remnants could be identified. The surgical anastomosis between the right subclavian artery and the right



Fig. 1 Admission hest -ray showing decre se l pulmonary vasculature The cardiac image is slightly prominent.

Table I

Variables	Pressure (mm Hg)	O saturation ( )
Right tri m	ac 11 m 9	49
Right-sided (anatomic left) ventricle	120/7 E D	39
Left trium	ac 5 m 3	55
Left-sided ystemic (anatomic right) ventricle	84/6-9 E.D	62

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Discussion

Corrected transposition of the great vessels seldom exists w thout complicat

Pulmonary atresia and intact ventricular septum complicating corrected transposition of the great vessels

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Kent Ellis M.D
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This report presents a unique example of pulmonary atresia with intact ventricular septum complicating corrected transposition of the great vessels The correct anatomic diagnosis was made by angiocardiography Prominent filling of the coronary arterial system occurred via sinusoids in the wall of the small blind right sided pulmonary (anatomic left) ventricle

Case report

M O a three and one-half month old Caucasian infant was admitted to Columbia Presbyterian Medical Center on Feb 25 1969 with a history of progressive cyanosis since 3 days of age The infant was the product of a normal pregnancy and was delivered at another institution by elective caesarean section The birth weight was 7 pounds and 10 ounces Cyanosis was first noted at 3 days of age but no murmur was heard and the baby was discharged on the fifth hospital day

One week prior to admission the patient became extremely irritable the cyanosis deepened and the respiratory rate increased

On admission physical examination revealed a well developed Caucasian female infant with tachypnea moderate intercostal retractions, and marked cyanosis. The heart rate was 100 per minute and the respiratory rate was 60 per minute The lungs were clear there was no hepatosplenomegaly or peripheral edema. The pulses were equal in all extremities. The significant findings of the cardiac examination included a quiet precordium without a prominent ventricular impulse a second heart sound of normal intensity and single at the left upper sternal border and a Grade 1 2/6, soft, continuous murmur heard at the left base and under the left clavicle

The hematocrit was 58 per cent and the arterial O_2 saturation was 43 per cent

X-ray examination of the chest (Fig. 1) showed minimal cardiac enlargement and decreased pulmonary vascularity The electrocardiogram (Fig 2) revealed a frontal plane axis of +60 degrees with peaked P waves in Leads II and aVR Q waves were absent in the precordial leads. There was no evidence of ventricular enlargement

Cardiac catheterization was performed in room air under local anesthesia Both ventricles were entered the left-sided systemic (anatomic right) ventricle via an interatrial communication. Radiopaque contrast material injected into this ventricle showed the aorta arising anteriorly along the left heart border as is typically seen in corrected transposition of the great vessels (Figs. 3A and 3B) A patent ductus arteriosus was the sole source of pulmonary blood flow and filled the main pulmonary artery The pulmonary vessels were small.

From the Department of Pediatrics, Radiology and Pathology College of Physicians and Surgeons, Columbia University and the Columbia-Presbyterian Medical Center New York, N Y
This work was supported by Training Grant 5 T01 HD00127-04 and Grant HE 05189-10 of the National Institutes of Health.
Received for publication June 5, 1970.
Reprint requests to Carl N Steeg, M.D., Cardiovascular Laboratory Columbia-Presbyterian Medical Center 622 West 168 St., New York, N Y 10032.

Angiocardiographic study of the right-sided pulmonary (anatomic left) ventricle revealed a hypoplastic chamber with no direct connection to either the great vessels or the other ventricle. Dilated myocardial sinusoids in the wall of this small cavity were opacified. These retrogradely filled the coronary arterial system and faintly opacified the ascending aorta (Fig. 4, A and B). These studies were interpreted as showing corrected transposition of the great vessels with pulmonary atresia, intact ventricular septum, and hypoplasia of the blind right-sided pulmonary (anatomic left) ventricle. The catheterization data are included in Table I.

Two days following cardiac catheterization, a right-sided subclavian artery–pulmonary artery anastomosis was performed. Following this procedure, the infant showed initial improvement. On the sixth postoperative day cyanosis suddenly became more intense and the baby became more irritable. Before an atrial septostomy or second systemic-pulmonary shunt could be attempted, cardiac arrest occurred, and the patient could not be revived.

Pathology

The heart was noted to be markedly enlarged, weighing 50 grams and consisting predominantly of the left-sided ventricle. The aorta arose anteriorly and to the left of the pulmonary artery (Fig. 5). Both atria appeared dilated. A patent foramen ovale was noted which measured 0.8 cm. in diameter. A 0.3 cm. secundum atrial septal defect was also present. The right-sided atrioventricular valve was bicuspid and markedly hypoplastic, the annulus measured 0.6 cm. in circumference. The small cavity of the right-sided ventricle was lined by thick white endocardium.

The myocardium was hypertrophied, measuring 1.4 cm. in thickness. No pulmonary outlet from this chamber was present and the ventricular septum was intact. Small sinusoidal openings were visible within the ventricular myocardium.

The 4 pulmonary veins entered an enlarged left atrium in the normal fashion. The left atrioventricular valve was tricuspid and the annulus markedly dilated, measuring 6.0 cm. in circumference. The septal cusp was adherent to the septal wall, and crista supraventricularis separated the medial cusp from the aortic valve (tricuspid-aortic discontinuity). The endocardial surface was coarsely trabeculated, characteristic of an anatomic right ventricle. The chamber was grossly dilated, but the myocardium was only slightly hypertrophied, measuring 0.7 cm. in thickness.

The ascending aorta was large and the coronary arteries were transposed. The right coronary artery arose from the anterior aortic sinus and gave rise to the anterior descending coronary artery as is usually the case in corrected transposition of the great vessels. The left coronary artery originated from the posterior coronary sinus and descended in the posterior interventricular groove. The pulmonary artery was posterior and had a circumference approximately one third that of the aorta. The pulmonary orifice was atretic and no valve remnants could be identified. The surgical anastomosis between the right subclavian artery and the right



Fig. 3. Admission chest x-ray showing decrease in pulmonary vasculature. The cardiac image is slightly prominent.

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E.D. = end-diastolic pressure in mm. Hg.

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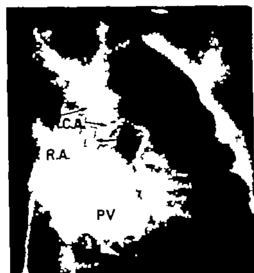
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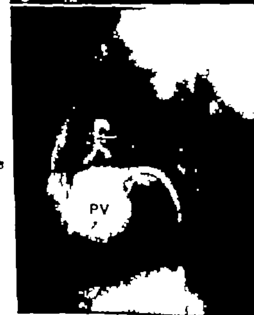
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A



B

Fig. 4 *A* and *B*. Frontal and lateral views, respectively. The catheter is in the small right-sided pulmonary (anatomic left) ventricle (*P.V.*). With opacification of this chamber some contrast material regurgitates across the atrio-ventricular valve into the right trium (*R.A.*) ... contrast material enters the pulmonary artery or the other ventricle indicating pulmonary atresia with intact ventricular septum. Virtually the entire coronary arterial system is opacified via transmyocardial sinusoids. Retrograde coronary artery flow mainly via branches in the interventricular and right atrio-ventricular sulci, fills major trunk (*C.A.*) which in turn, by retrograde flow opacifies large artery (*R.C.A.*) connected to the ascending aorta. The aorta (*AO*) and some of its branches are also faintly opacified.



Fig. 5 Frontal view of the heart at necropsy. The aorta (*AO*) arose anteriorly and to the left of the hypoplastic pulmonary artery (*P.A.*). The left-sided systemic (anatomic right) ventricle has been opened. The anterior descending coronary artery (a branch of the right coronary artery) is seen on the ventral surface.

cardiovascular anomalies. Frequent among these are ventricular and atrial septal defects and anomalies of the left atrio-ventricular valve including insufficiency, stenosis, atresia, and Ebstein's anomaly.[1-4]

Pulmonary stenosis (or atresia) together with a ventricular septal defect is common in corrected transposition.[1,2] Ellis and associates[11] found this combination of anomalies in about one third of their cases. In contrast, pulmonary stenosis *with intact ventricular septum* has been reported much less often in corrected transposition.[1,2]

Somewhat surprisingly, *pulmonary valve atresia with intact ventricular septum* complicating corrected transposition of the great vessels is evidently very rare, not having previously to our knowledge been diagnosed in life. Perhaps this rarity is related to the fact that in corrected transposition a ventricular septal defect is usually present, whereas in normal bulbo-

Fig 2 Admission electrocardiogram Rate of 140, sinus rhythm. Frontal plane axis = +60 degrees. Q wav are absent in the precordial leads.



Fig 3A Frontal angiocardiogram. Contrast material is seen filling the systemic left-sided (anatomic right) ventricle (*SV*) The large aorta (*AO*) can be seen ascending along the upper left border of the heart. The pulmonary artery has not yet filled from ... ductus arteriosus.



Fig 3B Lateral view taken 0.5 sec. later The *pulmonary artery (P.A.)* is *posterior to the aorta (AO* nd filled exclusively from a patent ductus arteri osus (arrow) A well-defined muscula infundibulun was found below the aortic valve.

Review

Total anomalous pulmonary venous return

A review and report of the oldest surviving patient

Jay B Jensen M.D
S Gilbert Blount J M.D
Denver Colo

Total anomalous pulmonary venous return (TAPVR) is a congenital defect resulting in the connection of all of the pulmonary veins to the right atrium or its tributary veins. As a result the entire systemic and pulmonary venous return enters the right side of the heart. This defect is compatible with life only because an atrial septal defect or patent foramen ovale is almost always associated thus allowing inflow to the left heart. Excluded from consideration in this paper are those cases wherein only part of the pulmonary veins drain abnormally to the right side.

Credit is given to Friedlowsky for the first description of TAPVR in 1868. Brody's[1] description of 37 cases collected from the literature in 1942 served to define and describe the clinical entity. In 1960 Burroughs and Edwards[2] analyzed 188 cases of TAPVR found in the literature and 75 cases seen in London were reported by Carter and co-workers[3] in 1969. An excellent anatomical study of 113 cases of partial and total anomalous venous connection is reported by Blake and co-workers. Cooley and associates[4] reported a series of 62 cases treated surgically and reviewed the surgical history of this disease. Other excellent general reviews of this problem are those by Guntheroth and colleagues[6] and Keith and colleagues.[7]

Although not common the incidence of this lesion is probably higher than was thought initially. In Abbott's review of 1,000 autopsy cases of congenital heart disease she found only four patients with TAPVR. DuShane at the Mayo Clinic found eight cases among 506 autopsies on infants and children with congenital heart disease and TAPVR was found in 0.8 per cent of over 1,500 autopsies done at the Children's Hospital of Pittsburg. Cooley and colleagues[5] report that this is the fourth most frequent cyanotic congenital heart lesion requiring surgery during the first year of life at Texas Children's Hospital. Edwards[11] points out that one reason for a falsely low incidence is that the heart and lungs are often separated early in the necropsy dissection making later identification of anomalous pulmonary veins very difficult.

It is the purpose of this communication to report 27 additional cases of TAPVR seen at Colorado General Hospital between 1951 and 1970. In this group the diagnosis was verified at autopsy in 18 cases, at

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ventricular loop development an intact ventricular septum is the rule One recent textbook of pediatric cardiology states that in corrected transposition pulmonary atresia apparently is always accompanied by a ventricular septal defect [8]

Remarkable opacification of the coronary arteries occurred in our patient on injection of radiopaque contrast material into the small cavity of the blind right sided pulmonary (anatomic left) ventricle The presence of dilated ventricular sinusoids connecting the ventricular cavity with the coronary arteries was documented at necropsy The probability that retrograde flow had occurred in life is also supported by the fact that the systolic pressure in this small ventricle was substantially higher than that in the aorta Further retrograde flow from the coronary arteries into the aorta is also well shown in Fig 4 A and *B* Such retrograde filling of the coronary arteries via dilated transventricular sinusoids has been recognized in cases of pulmonary atresia with intact ventricular septum not associated with corrected transposition [13]

Summary

A three and one half month old infant with corrected transposition of the great vessels pulmonary atresia and intact ventricular septum is presented Cardiac catheterization and angiocardiography disclosed a small blind right sided pulmonary (anatomic left) ventricle with systolic pressure exceeding systemic levels. The chamber communicates with the coronary arterial system via transmyocardial sinusoids

To our knowledge this is the first report of this syndrome complex diagnosed during life

The authors wish to express their sincere appreciation to Dr William A. Blanc who reviewed the pathology and to Dr Mary Jane Jesse the patient private physician, for allowing us to publish this data.

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nary veins will drain into the portal vein ductus venosus, inferior vena cava or some tributary of these veins.

Pathologic anatomy

The main features of the pathologic anatomy of the various types of abnormal pulmonary venous drainage are easily understood when considered in light of their embryologic derivation. It has been pointed out by Blake and associates[4] that although a majority of these lesions fit into a few discrete categories there is a broad anatomic spectrum in this disorder with a large variety of communication patterns being seen. These and other authors point out that a distinction should be made between anomalous drainage and anomalous connection. They cite examples in which hemodynamic studies indicate normal drainage but where anomalous connections were found at surgery. This apparent paradox is due to preferential streaming of pulmonary venous blood from right to left across the atrial septal defect and thus entering the left atrium even though the pulmonary veins or the vessel carrying pulmonary venous blood may be connected to the right atrium. This situation is most commonly seen in cases of partial anomalous pulmonary venous connection.

Total anomalous pulmonary venous drainage may occur as one of several major cardiovascular anomalies or as an isolated lesion with only the associated interatrial communication which is mandatory for survival of the patient. Also grouped with this latter uncomplicated group are those cases in which the only other lesion is a patent ductus arteriosus. In our series of 27 cases, four patients (15 per cent of the group) had a major associated cardiovascular abnormality and one patient had mirror-image dextrocardia but was without other anatomical defects. The cases with complicated lesions in our group include one patient with a hypoplastic aorta, one with a tetralogy of Fallot, one with a ventricular septal defect and an aortic coarctation and a fourth patient with dextroversion A V communis, a patent ductus arteriosus, and an atretic pulmonary valve. The incidence of complicating lesions in the 188 patients of Burroughs and Edwards[3] was 35 per cent while 23 per cent of the 75 patients of Carter and associates[3] were noted to have another major cardiovascular anomaly. None of our patients with drainage to the coronary sinus had complicating lesions. This is similar to the observations of Burroughs and Edwards.[3]

Darling and co-workers[14] subdivided the cases of TAPVR into four types, depending upon the level of the abnormal drainage. In Type I supracardiac connection the drainage is through the right superior vena cava or alternatively through a remnant of the left anterior cardinal vein which drains into the innominate vein. Type II lesions include those with pulmonary veins that drain at the cardiac level either into the right atrium directly or through the coronary sinus. In Type III connections the drainage is infradiaphragmatic via a common channel which descends anterior to the esophagus passes through the diaphragm and enters the portal vein or less commonly the ductus venosus the inferior vena cava or another portal tributary. In one unusual case of this type the drainage was via a left gastric vein and the patient presented with fatal hemoptysis from gastric varices.[1] The Type IV lesions are classified as those in which drainage is to multiple levels. The location of the drainage site in our series and in those of Cooley and colleagues,[3] Burroughs and Edwards,[3] and Carter and colleagues[3] is presented in Table I. It is seen that for the combined group of 343 patients, a persistent left anterior cardinal vein was the most common drainage site being present in 38 per cent of the total number. Drainage was into the coronary sinus in 16 per cent, to the right atrium in 14 per cent, to the right superior cava or its tributaries in 14 per cent and to an infradiaphragmatic site in 12 per cent of the cases. The location of drainage sites was multiple or unspecified in 7 per cent of cases.

The size of the interatrial communication is an important anatomical feature which determines the amount of flow through the systemic circuit. This opening varies from a patent foramen ovale as small as 1 to 2 mm to secundum atrial septal defects of

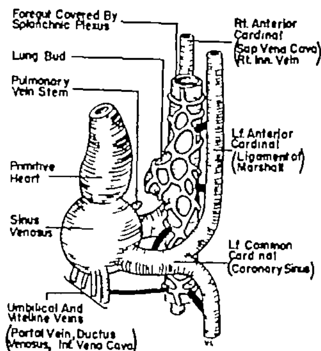


Fig. 1. Diagram showing embryologic development of pulmonary venous connection. In black are the normal communications between the pulmonary venous plexus and surrounding vein in the embryonic heart. (Reproduced by permission of the American Heart Association, Inc., from Gott, V. L., Lester, R. G., Lillehei, C. W., and Varco, R. L.: Circulation 13:543, 1956.)

operation in three patients and by catheterization and/or angiography in six patients. Included in this group is a man 46 years of age who is the oldest reported surviving patient with this lesion. A review of the clinical, hemodynamic, and surgical features of our cases is presented and compared with other series in the literature.

Embryology

The lung develops as an outpouching from the ventral aspect of the foregut, as is illustrated in Fig. 1. The splanchnic plexus covering the foregut is the anlage of the venous plexus which covers the lung bud and the common pulmonary vein develops as an outpouching from the dorsum of the sinus venosus.[13] The pulmonary venous plexus surrounding the lung bud then develops a communication with this common pulmonary venous channel. The opening of the common pulmonary stem, originally in the center of the sinus venosus, shifts to the left as the interatrial septum develops so as to drain into the left atrium. The final step in this process is the absorption of the common channel into the left atrial wall so that all four of the tributary pulmonary veins enter the atrium separately.[13]

Embryonic connections exist between the splanchnic plexus which becomes the pulmonary venous plexus and the nearby systemic and visceral veins. One group of connections is with the cardinal system which is the anlage of the superior vena cava, innominate vein, coronary sinus, and azygos vein. The second group of communications is with the umbilical and vitelline veins which later become the inferior vena cava, portal vein, and ductus venosus. Normally the connections with the cardinal and umbilicovitelline systems regress as the connection between the pulmonary plexus and the common pulmonary vein develops.

Various faults in the course of events just described can result in any of several abnormalities of pulmonary venous drainage. These abnormalities and the mechanism of their development have been classified by Neill.[14]

If the interatrial septum grows abnormally far to the left, the pulmonary veins enter the right atrium directly. In this situation, no abnormal communications persist with the cardinal or umbilicovitelline systems and the pulmonary venous plexus establishes a normal connection with the common pulmonary venous trunk.

In all the other types of abnormal pulmonary venous drainage there is failure of the common trunk to connect with the pulmonary venous plexus plus persistence of one or more abnormal connections of the pulmonary venous plexus with the cardinal or umbilicovitelline systems. If the persistent connection is with the left cardinal system, the pulmonary drainage will be either through a persistent vertical vein to the left innominate vein or through the coronary sinus. In the former situation the proximal portion of the left anterior cardinal vein regresses; in the latter the more distal portion of this vein regresses. If the persistent connection is with the right cardinal system the pulmonary veins will drain into the azygos vein or the right superior vena cava. When the connection of the pulmonary plexus with the umbilicovitelline system persists the pulmo-

sociates[11] found that the ductus was patent in 23 per cent of 60 cases.

Of considerable interest are the pulmonary vascular changes noted in this entity. Dilatation of veins and medial muscular hypertrophy in small pulmonary arteries and arterioles are common findings whereas intimal changes are infrequently found. Changes in the media were noted in five of our cases. One of these patients had severe obliterative pulmonary vascular changes similar to those in a case reported by Levy and co-workers.[21] Unlike that patient, ours had a ductus arteriosus that was completely closed.

Clinical presentation

The clinical picture presented by patients with TAPVR represents a broad spectrum which varies from the severely ill cyanotic newborn infant to the less cyanotic and minimally disabled adult. This diversity is vividly illustrated by three patients recently seen at our hospital.

Case 1. G. M. (CGH No. 370743) a female infant, the product of a normal pregnancy and delivery was noted to be cyanotic with crying on the first day of life. A murmur was noted on the third day, at which time the patient was transferred to Colorado General Hospital.

Physical examination at that time revealed an infant in moderate respiratory distress, breathing 30 times per minute. The pulse was 140 and peripheral pulses were of good quality. The precordium was slightly hyperactive. The second sound was accentuated at the base, was detectably split, and did not clearly vary with respiration. There was a soft grade 2/6 nonobstructive systolic murmur heard best at the second left interspace.

The electrocardiogram (ECG) showed possible right ventricular enlargement and the chest x-ray showed mild increase in vascularity and normal-sized heart.

On the fifth day of life evidence of congestive heart failure appeared and cardiac catheterization and angiocardiography were done. These showed TAPVR with drainage to a persistent left anterior cardinal vein, a large atrial septal defect, and a patent ductus arteriosus.

On the sixth day of life the patient deteriorated further with increasing hypoxia and congestive heart failure despite continued medical treatment. Because of this the patient was operated on at that time. With the patient on full cardiopulmonary bypass an anastomosis between the common pulmonary venous channel and the left atrium was performed and the persistent left anterior cardinal vein was ligated and divided.

The patient tolerated the procedure well and appeared somewhat improved over the preoperative status. However, on the second post-the left suddenly had cardiac arrest and died.

Case 2. M. J. (CGH No. 92003) was a 46-year-old man who was first noted to be cyanotic and in whom the presence of heart disease was first recognized at the age of six years. He suffered from frequent attacks of pneumonia and respiratory infections during childhood. The patient has led a relatively normal life including marriage, rearing two children, and having a responsible job. He has participated in dancing, tennis, and biking although he recognizes that his exercise tolerance is less than that of normal family members. At age 33 he began having supraventricular tachyarrhythmia for which he received quinidine. He was first seen at our hospital then and the diagnosis of TAPVR with drainage via a persistent left anterior cardinal vein was made at cardiac catheterization. Later that same year he developed symptoms suggestive of a cerebrovascular accident but these cleared without residual deficit. There have been no similar recurrences. The patient noted the onset of fluid retention, increasing dyspnea on exertion, and paroxysmal nocturnal dyspnea in January 1970. These became worse and he was seen by us in April 1970.

At that time the pulse rate was 105, the blood pressure was 122/96, and respirations were 29 per minute. The pulses were small in volume and pulsus alternans was present. There was elevation of the jugular venous pressure, marked cyanosis and moderate clubbing. Marked peripheral edema was present. The chest was increased in AP diameter with a pectus carinatum deformity. There was marked increase in precordial activity at the left and right of the sternum and at the apex. There was a palpable third heart sound. On auscultation the second sound was faint but widely split and fixed. Both third and fourth sounds were present. There was a soft short scratchy midsystolic murmur heard best at the left upper sternal border.

The ECG revealed marked right atrial enlargement, marked right axis deviation, and right ventricular enlargement. The chest x-ray is shown in Fig. 2.

The patient was admitted to the hospital and treated with digitalis and diuretics, with improvement in his status. He was then discharged and returned home.

Case 3. D. L. (CGH No. 255995) a male child was well until the age of six months when he had an episode of pneumonia. A heart murmur was first noted at that time. He continued to have frequent respiratory infections and because of this he was evaluated at Colorado General Hospital in February 1966, at the age of 17 months. At that time cardiac catheterization was performed which revealed TAPVR with drainage through the coronary sinus into the right atrium. Over the next four years the patient grew and developed very poorly and began to display mild cyanosis on exertion. In addition he tolerated exertion poorly and was noted to be dyspneic when playing. Because of these factors the patient was admitted to Colorado General Hospital on May 18, 1970, for surgical correction.

Physical examination at that time revealed a small, poorly developed boy weighing 31 pounds. The pulses were normal. Prominent a and "v" waves were noted in the neck veins. The left pre-

Table I. Drainage site of anomalous veins in TAPVR (including complicated lesions)

	No. of cases				Total	
	Burroughs and Edwards[3]	Cooley et al.[5]	Carter et al.[6]	CGH series*	No.	Per cent
Supracardiac						
LACV†	56‡	28	34	12	130	38
RSVC	31	7	7	2	47	14
Cardiac						
RA	30	8	3	6	47	14
CS	18	12	20	5	55	16
Infradiaphragmatic						
Portal, IVC, DV, etc.	28	3	8	2	41	12
Multiple and other	16	4	3	0	23	7
Total	179	62	75	27	343	

*CGH, Colorado General Hospital.
†LACV, left anterior cardinal vein; RSVC, right superior vena cava; RA, right atrium; CS, coronary sinus; IVC, inferior vena cava; DV, ductus venosus.
‡Figures indicate number of cases except where percentage is specified.

large size. Anatomical description at operation and autopsy was detailed enough to determine this factor accurately in only a minority of our cases.

The anatomy of the common pulmonary venous channel is an important factor in determining pulmonary venous pressure and secondarily pulmonary arterial pressures and pulmonary flow. In most instances this is a capacious channel but cases in which it is constricted or compressed have been reported. Burroughs and Edwards[3] have emphasized the importance of the length of this channel. Patients with a long channel such as those in the group with infradiaphragmatic drainage tend to have higher pulmonary venous and arterial pressures than those with shorter common channels. In our series there was no localized narrowing or compression of the common vein described; however, it is common for veins draining into infradiaphragmatic locations to be obstructed by external compression or localized constriction.[17,18] In addition to constrictive lesions and long length of the venous channel, the interposition of the liver into the pulmonary venous return circuit may be an important factor in increasing resistance to flow and causing pulmonary venous hypertension. Less commonly there may be constriction or compression in patients with drainage into a persistent left anterior cardinal vein.[19,20] This most usually results from external compression of this vein between the pulmonary artery and the left main bronchus. However, on occasion this may be due to a localized constriction of the vertical vein at its junction with the left innominate vein.

The size of the left atrium and left ventricle are important factors in TAPVR, especially when surgical correction is planned. In many cases these structures are hypoplastic, probably due to the decreased volume load which is presented to them. These structures were felt to be smaller than normal at operation or autopsy in seven of our patients. The waist of the left atrial appendage is commonly smaller than the common pulmonary vein.[7] This was a factor of more importance with older surgical approaches when the appendage was used as an anastomotic site.

The ductus arteriosus was widely patent enough to allow passage of a probe in six of our patients at the time of operation or postmortem examination. Darling and as-



Fig. 3. PA and lateral chest x-ray of D. L., 6-year-old boy with TAPVR and drainage into the coronary sinus. Note the indentation of the coronary sinus on the barium-filled esophagus in the lateral view.

Table II. Age spectrum in TAPVR (age at death, operation, or last follow-up)

Age (yr.)	Number of cases				Total	
	Keith et al.	*Carter et al.*	*Cooley et al.*	*CGH series*	*No.*	*Per cent*
Below 1	47	58	35	16	156	70
1-2	0	5	5	2	12	5
2-10	10	10	17	8	45	20
11-20	0	2	4	0	6	3
Above 21	1	0	1	1	3	1
Total	58	75	62	27	222	

exemplified by our first patient. In the second group, difficulties with congestive heart failure are later in appearance and during their early years these patients may show minimal outward evidence of cardiac disability. Our second and third patients are representative of this group, which constitutes a minority of the patients with TAPVR.

The tetrad of cardiac enlargement, cyanosis, fixed splitting of the second heart sound, and increased pulmonary perfusion, which is almost pathognomonic of TAPVR, is commonly present in the older patients but is absent in the majority of the neonates and infants with this lesion.

The difficulty of detecting splitting of the second heart sound in the very young infant with a rapid heart rate obviously is one factor which limits the usefulness of this constellation of findings in this age group. Thus infants without this tetrad but with evidence of even slight cyanosis and radiographic evidence of cardiomegaly or congestive heart failure should be suspected of having TAPVR and investigated accordingly.[4]

In our series the onset of congestive



Fig. 2. PA and lateral chest x ray of a 46-year-old man (Case No. 2) with TAPVR draining through a persistent left anterior cardinal vein showing cardiomegaly increased pulmonary perfusion, and the typical snowman configuration.

cordium was prominent and the entire precordium was hyperactive with a marked right ventricular lift. The second heart sound was widely split and did not close with expiration and the pulmonic component was accentuated Heard best in the second left interspace was a grade 3/6 harsh ejection-type murmur which was radiated toward the back and the left shoulder A low-pitched grade 3/6 rumbling diastolic murmur was heard best at the lower left sternal border

The electrocardiogram revealed right atrial and right ventricular enlargement and right axis deviation The chest x-ray is shown in Fig 3

On May 22 1970 the patient s lesion was surgically corrected with the use of full cardiopulmonary bypass. An atrial septal defect with an estimated diameter of 2 cm. was enlarged and a patch of pericardium was sewed over the defect and the ostium of the coronary sinus so as to deflect all of the pulmonary venous return to the left atrium. The patient tolerated the operation well recovered rapidly and was discharged on the tenth postoperative day

The clinical course of G M (Case 1) is unfortunately more typical of this disease with death occurring prior to the end of the first year The second patient illustrates the fact that these patients can rarely survive to adult life We were able to find reports of four patients who have survived beyond age 30 [11,22,23] The oldest reported patient was one who died at 42 years of age [22] and thus our patient at age 46 represents the oldest reported patient with TAPVR

In our series 70 per cent of the patients were male and 30 per cent were female This compares with an incidence of 57 per cent male and 43 per cent female patients in a combined group of 268 patients from three other series [3,4,7] The age spectrum of TAPVR is shown in Table II where our series and three other series are tabulated The ages noted are those at the time of death operation or last follow-up It is seen from this that 70 per cent of the patients seen with this disease are less than one year old 25 per cent are between one and ten years of age and only one per cent are over age 20 This reflects the very high rate of early deaths which has been stated to range from 70 to 80 per cent during the first year [3] Thus it is apparent that any surgical therapy must be applied very early in life if an appreciable percentage of these children are to be salvaged

The clinical presentation in TAPVR tends to vary from patient to patient but in general they can be grouped into two categories depending upon the time of onset of congestive heart failure [3] One group presents with congestive heart failure very early in life and suggests a differential diagnosis which includes transposition of the great vessels aortic hypoplasia coarctation or atresia of the aorta truncus arteriosus and other lesions causing early cardiac decompensation [7] This group is

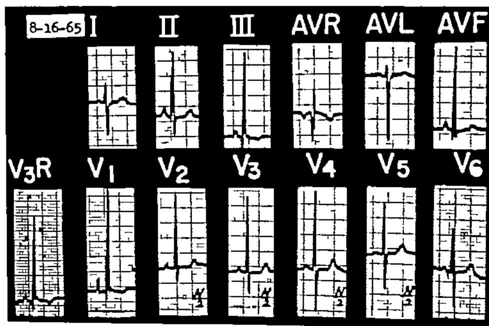


Fig. 4 Electrocardiogram of R. G., 3-year-old boy ith TAPVR nd drainage via persistent left anterior cardinal vein. The record show right axis deviation, right trial and ri ht ventricular enlargement.

and fixed and in seven patients splitting of the second sound could not be detected

Murmurs are not consistently present in patients with TAPVR even when present they are in no way diagnostic or charac teristic. The most commonly described murmurs are short, soft systolic murmurs that are nfrequently accompanied by a thrill They are most commonly located along the left sternal border in the second through the fourth interspaces. Tricuspid insufficiency and rapid turbulent pulmonary arterial flow are possible explanations as to the genesis of these systolic murmurs. Keith nd co-workers noted a soft continuous murmur with the qual ty of a venous hum in the pulmonary area in several patients with drainage to the left anterior cardinal vein. This finding has not been verified by other authors. Scott and Welch[38] felt that a continuous murmur is a finding which is often associated with anatomical obstruction to pulmonary venous flow Some patients will have low frequency diastolic m rmurs with or w th out a presystolic component at the apex or lower left sternal border These murmurs are probably generated by high flow across the tricuspid valve Guntheroth and colleagues noted absence of these diastolic murmurs in patients with infradiaphragmatic drainage This is probably because of the relatively low pulmonary flow in these patients with a resultant smaller flow across the tricuspid valve

Twelve of our 27 patients had only systolic murmurs four had both diastolic and systolic murmurs, and three had continuous murmurs. The character and location of these murmurs were similar to those described by others. All three patients with continuous murmurs had drainage via persistent left anterior cardinal veins but no evidence of obstruction to pulmonary venous flow was found at postmortem examination in any of the three.

Electrocardiogram and vectorcardiogram

The ECG in patients with TAPVR almost universally shows right ventricular enlargement right axis deviation and, less consistently right atrial enlargement. A typical ECG is shown in Fig 4 An exceptional patient with a complicating endocardial cushion defect may fail to show right axis deviation[38] DuShane and coworkers[41] pointed out that a common atrium is a more usual cause for left axis deviation and a counter-clockwise QRS

heart failure could be dated in 16 patients and it occurred prior to the age of six months in 13 or 81 per cent of the group All of these 13 infants were dead by the age of 18 months and 12 were dead prior to reaching one year of age This corresponds to the experience of Cooley and associates,[8] who state that if congestive heart failure appears during the first six months of life the chances of survival to childhood are poor In our series six patients survived beyond one year and were alive at the time of last follow up when their ages were 2½ 4½ 6 8 9 and 46 years respectively In none of these patients was congestive heart failure an early occurrence Surgical treatment has been carried out in four of these patients can not be done because of irreversible pulmonary hypertension in another and was not advised for the patient who is 46 years of age Four of these six patients have drainage to a persistent left anterior cardinal vein in the other two drainage is to the coronary sinus

Features which are commonly present in children with TAPVR include cyanosis tachypnea labored respiration poor feeding frequent respiratory infections and slow weight gain In all but the oldest of our patients body size was smaller than would be expected for their age Dyspnea and cyanosis may be intensified with feeding It is felt by some that this is a more frequent finding in patients with infradiaphragmatic drainage [14] It is postulated that this occurs because the common venous channel accompanies the esophagus through the diaphragm and that the channel is compressed during feeding

The presence of cyanosis was commented on in 20 of our patients and it began prior to one month of age in 19 of these In about one third of these patients the cyanosis was only intermittently present with feeding crying or other exertion

The degree of cyanosis in patients with this entity is quite variable Our experience of early death in those with early cyanosis is borne out by others.[2,14] It has been pointed out by Burroughs and Edwards[2] that patients with small intra-atrial communications and long common pulmonary venous channels tend to have an earlier onset of cyanosis. It has also been noted that patients with infradiaphragmatic connections tend to have more severe systemic hemoglobin oxygen desaturation than is present in other types In our series the systemic saturation varied from 62 to 85 per cent with a mean of 74 per cent in those with drainage above the diaphragm. In the one patient with portal drainage in whom arterial oxygen saturation was measured it was 31 per cent Keith and coworkers[7] reported a mean saturation of 88 per cent in 13 patients in whom it was measured and they pointed out that the values were such that clinical cyanosis would not be recognized in many of the patients Gott's group[13] reported saturations ranging from 69 to 93 per cent

The degree of oxygen saturation will be greater in patients with pulmonary blood flow which is high In this situation the proportion of highly oxygenated blood returning to the right atrium will be large relative to the amount of desaturated systemic blood returning to this chamber As a result the saturation in the right atrial mixing chamber will be higher as will be that of the blood which is shunted across the interatrial septum to the systemic circuit

The physical examination in patients with TAPVR displays the same spectrum of variability as does the clinical course. Hepatomegaly tachycardia tachypnea and other signs of congestive heart failure may be either present or absent. The peripheral pulses tend to be of normal quality unless a patent ductus, a complicating lesion or severe congestive heart failure is present The precordium may show evidence of right ventricular overactivity depending upon the age pulmonary flow and pulmonary resistance The pulmonary component of the second sound tends to be accentuated widely split and without respiratory variation The presence of these auscultatory findings in a cyanotic patient should immediately suggest the diagnosis of TAPVR Unfortunately these findings are often absent especially in the very young where such a helpful clue is most needed Comments as to the nature of the second sound were made in 22 of our patients. The pulmonic component was felt to be accentuated in 21 of them In nine patients the splitting was felt to be wide



Fig. 4 PA chest -ray of R. R., 7 month-old boy ith TAPVR nd drainage int the right trium. Note the cardiomegaly and congested lung fields.

characteristic x ray appearance However this is not as specific as the roentgenogram in the previously mentioned lesion. These patients have a heart that is normal in size and configuration w th the associated pattern of pulmonary venous engorgement. This is contrasted w th the appearance of a large heart and the pattern of increased pulmonary perfusion in all of the other patients with TAPVR.[38] This discrepancy of a normal-sized heart with clinical and roentgenographic features of congestive heart failure a cyanotic newborn should suggest th diagnosis. An example of such a chest x ray is seen in Fig 5 The differential diagnosis most often entertained in these patients includes the pulmonary causes of respiratory distress in infancy but should also include cor triatriatum stenosis of the pulmonary veins, nd mitral atresia.[34] Frequently the possibil ty of a primary cardiac difficulty is not entertained because of the absence of cardiomegaly In both of our patients with drainage into the portal vein the heart size was normal and the x-rays were read as showing granular opacities or pulmonary infiltrates.

Drainage at the atrial level either through the coronary sinus or directly into the right atrium presents a picture of increased pulmonary perfusion and cardiomegaly An example of such an x ray is shown in Fig 6. In addition to cardiomegaly and increased perfusion patients with drainage via the coronary sinus may show a characteristic indentation of the barium-filled esophagus where the large coronary sinus passes anterior to it. The curvature of this indentation is smaller than that caused by left atrial enlargement and is best seen in the lateral view. This is illustrated in Fig 3 Gott and co-workers[13] pointed out that the cardiac silhouette produces a boxlike shadow in some patients with drainage at the cardiac level but this is a nonspecific finding and is seen in many patients with right-sided lesions and



Fig. 5. PA chest x ray of L. S., a 1 month-old boy with TAPVR and drainage via the portal vein. Note the congested lung fields and normal sized heart.

loop in the frontal plane in the presence of a clinical picture like that of TAPVR. They feel that the QRS axis and direction of the loop are the most helpful features in differentiating these two entities.

It has been pointed out by Hastreiter and colleagues[17] that the patients with obstruction to pulmonary venous return frequently lack the tall peaked P waves indicative of right atrial enlargement. This is probably due to the smaller additional volume load on the right atria of these patients than in those without obstruction. Keith and his group[7] reported a higher incidence of right precordial q waves in TAPVR than in other types of congenital heart disease. This was not verified by Gessner and associates[16] and Guntheroth and associates.[8] The latter authors suggested that in some of the patients with q waves the pattern may have actually been an rsR′ with an isoelectric r. Vectorcardiograms done by Guntheroth verified that this is true in at least some cases. Small or absent R waves over the left precordial leads have also been noted in some patients, most commonly those with pulmonary artery pressures in excess of systemic.[8] Vectorcardiograms characteristically show clockwise loops in the frontal and horizontal planes and other findings suggestive of right ventricular enlargement.[16]

Electrocardiographic information is available in 19 of our patients. Eighteen of these patients had definite right ventricular enlargement. In one patient who died at age eleven days the presence of right ventricular enlargement was less definite. In all 19 cases the mean QRS axis was greater than 90° and it was greater than 120° in 12 patients. Right atrial enlargement was present in 16 patients. One of the two patients with drainage into the portal system had no evidence of right atrial enlargement. Six patients showed relatively small R waves in the left precordial leads.

Chest roentgenography

The chest x ray is probably the most useful of the routine noninvasive diagnostic tools in making the diagnosis of TAPVR. This is particularly true in older patients with types of lesions in which the roentgenographic appearance is practically pathognomonic. The chest film is particularly helpful in the older patient with drainage to a persistent left anterior cardinal vein. These patients have a "figure-of-eight" or "snowman" appearance as exemplified by Fig. 2.[7] The upper half of the "8" is formed by a remnant of the left anterior cardinal vein as it ascends by the innominate and by the right superior vena cava as it descends to enter the right atrium. This classical appearance has been described in patients as young as nine weeks of age but it is usually not present until later in life. The sign is almost consistently absent in the very young infant in whom such a clue would be most helpful. In our 12 patients with drainage into a persistent left anterior cardinal vein, the classical "snowman" appearance was noted in five patients, the youngest of whom was 3 years of age. A wide superior mediastinum may also be produced by a true persistent left superior vena cava without anomalous drainage of the pulmonary veins, but the classical figure-of-eight pattern is absent.[7]

The group of patients with drainage below the diaphragm and any other patient with severe obstruction to pulmonary venous return also present a relatively



Fig. 8 Angiocardiogram from R. R., 7-month-old boy with TAPVR and drainage int the right trium. The injection was int the right ventricle and the frame on the left demonstrates pulmonary venous filling. The right frame shows the reopacification of the right trium from the pulmonary veins.

into the coronary sinus from that directly into the right atrium. Rowe and colleagues[19] have reported an angiographic sign which they feel is helpful in dist nguishing these two lesions. In the variety draining into the coronary sinus they noted an egg shaped opacification located over the spine with n the right atrial contour in the anteroposterior projection. W th d rect connections of the veins to the right atrium the entire atrium filled promptly appearing as a circular shadow but without the smaller oval opacity being present within ts contour We did not find this sign helpful in our series. An angiogram of a patient with drainage of the pulmonary veins directly into the right atrium is shown in Fig 8

In our series, 18 patients had angiog raphy and the diagnosis was correctly and unequivocally made in 13 of them. One patient was felt to have a ventricular septal defect and the anomalous pulmonary venous dra nage to the coronary sinus was not recognized No ventricular septal de fect was present at postmortem examina tion.

Cardiac catheterization and hemodynamics

Th first catheterization studies of pa tients with TAPVR were reported by Friedlich Bing and Blount[21] in 1950 The basic hemodynamic difficulty n this lesion is a large left to-right shunt through the anomalous veins and a right to-left shunt through an interatrial septal defect. The volume of systemic flow is dependent upon the size of the interatrial septal defect Anything that results in decreased pul monary perfusion will decrease the relative proportion of oxygenated blood return ng to the right atrium and will thus cause de saturation of the blood distributed to the systemic circulation It is because the pul monary flow exceeds the systemic flow that the systemic arterial blood is not markedly desaturated and has occasionally been reported to be within normal limits.[22]

The reasons for decreased pulmonary perfusion with resultant desaturation include pulmonary hypertension and rarely pulmonary stenosis.[23] The factors responsi ble for th development of pulmonary arterial hypertension include high pulmonary flow and more importantly obstructive lesions of the pulmonary venous system. There are numerous reports in the l terature of pulmonary arterial and arteriolar medial hypertrophy in TAPVR as a result of pulmonary hypertension. [11,24] To our knowledge our one patient and the one reported by Levy and associates[21] are the only ones in whom severe proliferative and obl terative ntimal changes have been present. In our patient these changes were present n the absence of an anatomically ... t ductus arteriosus. From this it is



Fig. 7. Angiocardiogram from C. C., a 6-year-old girl with TAPVR with drainage via a persistent left anterior cardinal vein. On the left is the venous phase of a right ventricular injection showing the persistent anterior cardinal vein draining into the innominate vein. On the right the catheter and injection are in the pulmonary veins via the innominate and persistent left anterior cardinal vein.

associated increased pulmonary blood flow.[4] In some of these patients there may be angular outpouching of the upper border of the right atrium, but this too is nonspecific. All of the patients in our series with drainage into the right atrium or coronary sinus had both cardiomegaly and increased pulmonary perfusion, and in Case No. 3 the specific diagnosis was suggested by the x-ray picture.

In patients where drainage of the pulmonary veins is into the right superior vena cava, cardiomegaly and increased vascularity are also present. The only additional clue which may be present is a somewhat broadened mediastinal shadow representing the superior vena cava on the right.

Angiocardiography has proved to be of great value in making the diagnosis of total anomalous pulmonary venous return. This method defines the anatomy in sufficient detail that it is of considerable assistance to the surgeon in helping him plan his surgical approach. In right atrial injections there is rapid opacification of the left atrium without dilution of contrast material in that chamber. This is followed by simultaneous opacification of the large pulmonary artery and the relatively small aorta.[21] The density of opacification of the aorta is equal to or greater than that of the pulmonary artery. In the venous return phase the anatomy of the pulmonary veins and the common pulmonary venous channel is outlined. The detail of the venous anatomy may also be seen by injecting directly into the common venous channel, as is occasionally possible. An example of this is shown in Fig. 7.

If the injection is made into a peripheral vein, the dilution of the opaque material by a jet of nonopacified pulmonary venous blood entering either the inferior or superior cava may provide another angiographic sign of the presence of anomalous pulmonary venous return.

The presence of obstruction to flow through the anomalous venous pathways can be suspected when (1) there is delay in emptying of the right side of the heart, (2) there is persistence of opacified blood in the pulmonary vascular system, and (3) there is failure to reopacify the right atrium.[21] The anatomy of anomalous pulmonary venous drainage to the portal vein can also be delineated by angiocardiography. These patients will show the abovementioned angiographic features of obstruction plus opacification of the anomalous venous channel with the contrast material accumulating in the area of the porta hepatis.[21]

It is difficult to differentiate drainage



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The reasons for decreased pulmonary perfusion with resultant desaturation include pulmonary hypertension and rarely pulmonary stenosis.[12] The factors responsible for the development of pulmonary arterial hypertension include high pulmonary flow and more importantly obstructive lesions of the pulmonary venous system There are numerous reports in the literature of pulmonary arterial and arteriolar medial hypertrophy in TAPVR as a result of pulmonary hypertension [1,22,26] To our knowledge our one patient and the one reported by Levy and associates[21] are the only ones in whom severe proliferative and obliterative intimal changes have been present. In our patient these changes were present in the absence of an anatomically patent ductus arteriosus. From this it is

tempting to speculate that a high flow low pressure left-to-right shunt of the type seen in uncomplicated atrial septal defects may occasionally lead to severe pulmonary vascular changes. This type of intimal lesion is usually seen only in the high pressure left-to-right shunts of ventricular septal defects and patent ducti. The possibility that the ductus was widely patent for a significant portion of our patient's life and then closed shortly prior to death is probably sufficient to vitiate these speculations.

The oximetry data obtained at cardiac catheterization are usually sufficient to suggest the diagnosis of TAPVR without added information. The characteristic findings include equal or nearly equal oxygen saturations in all four cardiac chambers[21,22] and the saturation in the pulmonary artery either equals or exceeds that in the aorta.[21] Preferential streaming of either pulmonary venous or systemic venous blood across the interatrial septum may cause exceptions to these rules.[4,22] The oxygen step-up as evidence of a left-to-right shunt may be seen at the right atrial level or in either vena cava. The hemoglobin oxygen saturations were very nearly equal in the pulmonary and systemic circuits in our patients with a mean difference of 2 per cent saturations and a maximum difference of 5 per cent.

It should be emphasized that the oximetry data, indicator dilution curves, hemodynamic findings, and clinical presentation in cases of common atrium can be almost identical to those in TAPVR.[22] As previously mentioned, patients with hemodynamics and clinical features of TAPVR but with ECG's suggesting an endocardial cushion defect are most likely to have a common atrium. An additional differential feature is that cases of TAPVR with connection at sites other than the coronary sinus and right atrium will have an oxygen step-up in either cava while no such step-up is seen with a common atrium.

Indicator dilution techniques are extremely helpful in making the diagnosis of TAPVR. Curves from right ventricular and pulmonary arterial injection sites will show a similar but abnormal configuration due to the marked degree of pulmonary recirculation and common mixing in the right atrium. The appearance time following pulmonary arterial or right ventricular injection is longer than that following right atrial or vena caval injection, thus demonstrating that the right ventricle is functionally upstream from the right atrium.[8] Systemic arterial sampling with injection into the right and left atria, respectively, will yield curves that are similar in appearance time and configuration except that there is an interruption of the downstroke of the curve from the right atrial injection. This is due to recirculation through the lungs of a portion of the medium.[22] It should be emphasized that the indicator curves with a common atrium may be identical to those in TAPVR.[22]

The systemic cardiac index is usually within the normal range and there are varying degrees of increased pulmonary blood flow and pulmonary hypertension. Right ventricular pressures often equal those on the left side but do not usually markedly exceed them.

Occasionally the diagnosis may be made by the catheter entering the pulmonary veins. This finding should be interpreted with care when the pulmonary veins are apparently entered from the right atrium. In this situation it is difficult to exclude the possibility that the catheter has passed across an atrial septal defect and into the pulmonary vein via the left atrium.[23] Differential dye dilution curves performed from the two main pulmonary arteries may be helpful in differentiating partial from total anomalous pulmonary venous drainage.

In assessing patients with TAPVR there are two often ignored hemodynamic features of great importance. These are (1) the interatrial pressure gradient and (2) the pressure gradient between the pulmonary wedge position and the right atrium. A significant interatrial gradient indicates a communication that is too small and a patient who would benefit from balloon or surgical septostomy.[23] The presence of a significant gradient between the wedge position and the right atrium indicates the presence of obstruction somewhere in the pulmonary venous circuit. This signals the need for careful analysis of the anatomy prior to embarking upon the course of surgical correction.[19,24]

Occasionally the site of obstruction in the pulmonary venous circuit can be localized by catheter pullback across sites of constriction or compression such as might be present in the left vertical vein at its junction with the left innominate or where it passes between the left main pulmonary artery and the left mainstem bronchus.

Cardiac catheterization was performed in 20 of our patients. Many of them were very ill and as a result complete hemodynamic and oximetry data are not available in all. Systemic and pulmonic blood flow and resistance data were obtained in too few patients to make any general conclusions. In general catheterization was successful in localizing the level of the anomalous connection and in all cases where full data were obtained the four cardiac chambers and pulmonary artery and aorta had saturation values very nearly equal to each other. Right ventricular pressures were measured in 15 patients; the systolic pressures ranged from 40 to 120 with a mean value of 85 mm. Hg. In two patients the right ventricular pressure exceeded the left ventricular pressure by more than 30 mm. Hg but it is not known how nearly simultaneously these pressures were measured. Two patients had interatrial gradients in excess of 4 mm. Hg but the size of their septal defects is not known. Wedge pressures were measured in only four patients and in one of these there was a difference of 16 mm. Hg between the wedge pressure and that in the right atrium. This patient had drainage to the coronary sinus and showed no evidence of pulmonary venous obstruction at autopsy examination and thus the validity of the gradient in this patient is in question.

Therapy

It is apparent from the very high and early mortality rates of medically treated patients with TAPVR that surgical treatment offers the only hope of improving the dismal outlook of the large majority. Surgical intervention is not without its limitations, however, as demonstrated by the surgical history of this disease and the high death rate still attending operation.

The first attempt to surgically correct TAPVR was made by Muller[20] in 1951 when a closed anastomosis between the left atrium and the common pulmonary venous channel was performed. In 1956 Lewis and associates reported a successful total correction in a 5-year-old patient under hypothermia and inflow stasis. Use of a semiopen atrial well technique was reported by Burroughs and Kirklin in 1956 and in 1957 Cooley and Ochsner[14] reported successful correction in a 6-month old infant with the use of cardiopulmonary bypass. These latter workers have had the largest experience in the surgical correction of this lesion, reporting results in 62 cases.[3] They use cardiopulmonary bypass in all of their cases. The use of surface-induced hypothermia has been advocated for treatment of TAPVR in the very young by Dillard and associates[44] in a report wherein they quoted their experience with seven patients under the age of 1½ years. The advantages cited as compared with cardiopulmonary bypass are the simplicity, minimal postoperative bleeding and minimal respiratory complications. The technique of balloon atrial septostomy in patients with TAPVR was reported by Miller and co-workers[45] in 1966. The use of this method is advocated only in cases with no extracardiac pulmonary venous obstruction and with a small intra-atrial communication.[46]

The principles of surgical repair as advocated by Cooley and colleagues[3] include (1) use of the pump oxygenator, (2) creation of the largest possible anastomosis between the common venous trunk and the left atrium, (3) closure of the atrial septal defect, and (4) ligation of the persistent left anterior cardinal vein, the connection to the right superior cava, or the connection with the portal system, whichever is present. Initially Cooley and Ochsner[14] advocated shifting the atrial septum to enlarge the underdeveloped left atrium so it could more readily accommodate the pulmonary venous return. However, presently they do not believe that this is necessary. Mustard and colleagues[47] have advocated a two-stage repair in which the drainage of the common trunk into the left atrium is performed initially and the closure of the septal defect and/or ligation of the common channel is done during a second operation. They believe that this gives the underdeveloped left heart an opportunity

Table III. TAPVR analysis of 12 patients treated surgically at Colorado General Hospital

Patient	*Age*	*Sex*	*Drainage site*	*Technique*	*Operation*	*Result*
G. M.	11 days	F	LACV	Bypass	Ligation, division and anastomosis of common vein to LA; no ASD repair	Died second day
A. L.	3 mo.	M	LACV	Inflow occlusion	Atrial septostomy	Died in hours
S. B.	2½ yr.	F	LACV	Inflow occlusion	Anastomosis common vein to tip of LA	Survived operation
C. C.	9 yr.	F	LACV	Bypass	Age 6, anastomosis of CV to LA; ligation CV Age 9, ASD closed	Survived; good result Massive CVA; alive
G. S.	3 mo.	M	LACV	Bypass	Anastomosis of CV to LA	Died in operation; anastomosis too small
G. H.	3 yr.	M	LACV	Bypass	Anastomosis of CV to LA; ligation of CV; closure of ASD	Died first day
J. S.	1 mo.	F	CS	Hypothermia; inflow occlusion	Ductus ligated; PA banded (diagnosis not recognized until after death)	Died in hours
J. F.	1½ yr.	F	CS	Hypothermia; inflow occlusion	Anastomosis of CS to LA	Alive; has CHB
D. I.	6 yr.	M	CS	Bypass	Flow redirected to LA	Alive
M. J.	8 yr.	M	RSVC	Bypass	Anastomosis of CV to LA, ASD repair, and repair of tetralogy of Fallot; ligation CV	Died first day
L. S.	1 mo.	M	PV	Bypass	Anastomosis of CV to LA and ligation of CV; no ASD repair	Survived operation; airway obstructed; died
M. W.	1½ mo.	M	LV	Bypass	Anastomosis of CV to LA and ligation of CV; ASD enlarged	Died first day

*LACV, left anterior cardinal vein; CS, coronary sinus; RSVC, right superior vena cava; PV, portal vein; CV, common vein; LA, left atrium; ASD, atrial septal defect; CHB, complete heart block; CVA, cerebrovascular accident.

to increase in size and capability prior to subjecting it to the total volume of pulmonary venous return. Cooley and his group[4] argued that the simpler first-stage operation has a mortality rate similar to that of total correction and that the latter should be done.

The repair done by Cooley on infradiaphragmatic drainage is similar to that done on patients with a persistent left anterior cardinal vein.[4] The common venous channel is anastomosed to the posterior aspect of the left atrium, and the venous channel which extends below the diaphragm is ligated and divided and the interatrial communication closed. If the veins enter the right atrium directly, these authors enlarge the interatrial septal defect and then suture a Dacron patch over the defect and around the pulmonary veins in such a way as to divert blood from them into the left atrium.[4] In patients where the common trunk joins the coronary sinus they use a different approach.[4] The remaining atrial septum between the coronary sinus and fossa ovalis is excised and an incision is made into the anterior wall of the coronary sinus, allowing its blood to empty into the left atrium. A Dacron patch is then placed over the septal defect which directs the pulmonary venous blood to the left atrium and obliterates the communication between the two atria.

Between 1961 and 1970 thirteen patients were operated on for TAPVR by the staff of Colorado General Hospital. The patients

Table IV. Surgical mortality rates in TAPVR (shown as per cent survival)

Drainage site	Mustard et al[17]		Rye et al[14]		Cooley et al		Present series		Total	
	No. of patients	Per cent survived	No. of patients	Per cent survived	No. of patients	Per cent survived	No. of patients	Per cent survived	No. of patients	Per cent survived
LACV*	20	40	39	51	28	68	7	29	94	52
RSVC	—	—	7	57	7	57	1	0	15	53
RA	—	—	9	100	8	62	—	—	17	83
CS	9	77	13	46	12	67	3	67	37	62
Other or unspecified	6	50	—	—	7	28	2	0	15	33
Total	35	58	68	57	62	61	13	31	178	56

*LACV, left anterior cardinal vein; RSVC, right superior vena cava; RA, right atrium; CS, coronary sinus.

ranged from 11 days to 9 years of age at the time of operation. Details regarding these patients and their treatment are shown in Table III. The pump oxygenator was used in ten patients and techniques of inflow occlusion and hypothermia were used in the remaining three patients. Four of the patients survived the operation (an operative mortality rate of 69 per cent). A patient operated on at the age of 18 months was the youngest to survive operation. Six patients were operated on prior to one year of life, all with a fatal result. Of the four surviving patients, one was lost to follow-up and another was doing well 18 months postoperatively despite persistence of postoperative complete heart block. A third patient did well for three years following partial correction of her defect but sustained a massive cerebral infarction and is a neurological cripple as a result of a second operation performed to close her atrial septal defect. The fourth patient (Case No. 3) is now doing well one month after operation.

One of the patients who died postoperatively did so because the anastomosis between the common vein and left atrium was too small. In another patient who died this anastomosis had thrombosed. One patient died of a postoperative airway obstruction. One patient had banding of the pulmonary artery and ligation of a ductus arteriosus because the correct diagnosis of TAPVR was not recognized. The lesion was thought to be a ventricular septal defect. This mistake was made because of incorrect interpretation of the right ventricular cineangiograms which were of suboptimal quality and which did not include late venous phase films. This serves to underscore the importance of obtaining good quality angiograms which include the late venous filling phase. The other operative deaths were due to either congestive heart failure, low cardiac output, or pulmonary complications.

It is of interest to compare the 13 patients who were operated on with the 14 who were not. Of the untreated patients, four (or 27 per cent) are still alive at the ages of 7 months and 6, 8, and 46 years. The eleven untreated patients who died did so at a median age of 5 months with a range of age from 11 days to 8 years. This is not to imply that this group of medically treated patients was similar to those who were operated on. In general the patients who had operations were very ill and got into trouble earlier in life than those who were not so treated.

The surgical mortality rates of our patients and those of three larger series[17,14] are presented in Table IV. Our over-all survival rate of 31 per cent is considerably lower than that reported by others. No explanation for this is apparent other than the fact that experience with a greater number of cases will probably tend to reduce the number of deaths. The over-all survival rate of 56 per cent in 178 cases is low but when this is viewed in the con

text of the natural history of the untreated disease it is seen that this does represent a significant accomplishment. In the four combined series the survival rates according to the site of drainage were: right atrium, 83 per cent; coronary sinus, 62 per cent; right superior vena cava, 53 per cent; left anterior cardinal vein, 52 per cent; and other or unspecified sites, 33 per cent. Thus it is seen that those patients with drainage at the cardiac level (either right atrium or coronary sinus) had a better survival rate (74 per cent) than those with drainage at the supracardiac level (53 per cent). In the series of Cooley and his group[8] there was less variation in mortality rates according to drainage site than in the others.

Although not specifically tabulated, successful surgical repair of infradiaphragmatic anomalous pulmonary venous drainage has been accomplished. This was first reported by Cooley in 1962 and since then several reports of survival have appeared, in one case at the age of five weeks. In general these children get into severe difficulty earlier than do patients with other types of TAPVR. The mortality rate for surgical treatment in this lesion is probably much higher than in other types. Despite this high risk it is generally agreed that an operation should be performed as soon as the diagnosis is made in these patients because of their universally poor outlook without operation and because of their rapid downhill course.[8,17,38,39]

The influence of cardiopulmonary bypass on surgical death rates was noted by Ryan and associates.[38] They found that the mortality rate in 25 patients whose operations were done on the pump-oxygenater was 24 per cent as compared with 53 per cent among 43 patients who were operated on without the benefit of this method. Dillard and colleagues[40] report a mortality rate of 43 per cent in seven patients all younger than 18 months who were operated on with surface-induced hypothermia. Although these numbers are small they seem to compare favorably with data from patients whose correction was done on cardiopulmonary bypass.

Of five patients aged 2½ months or less who had balloon septostomy, 80 per cent survived and have been followed for periods of from 3 to 22 months.[34] *Thus, in carefully* selected patients where the hemodynamic indications are clear, this seems to be a promising approach as it delays the need for definitive surgical treatment until an age when it can be done with less risk.

Cooley and co-workers[8,41] have thoughtfully analyzed various factors which affect the surgical mortality rate of patients with TAPVR. In general it can be said that factors which unfavorably influence the surgical mortality rate also adversely affect longevity in the medically treated patient. Age is a most important determinant of surgical mortality rate. This factor was analyzed for a combined group of 103 patients from our series and those of Cooley and colleagues[8] and Mustard and colleagues.[37] In 55 patients who were operated on below the age of one year the survival was 35 per cent; in 48 patients who had operations after one year of age the survival was 77 per cent.

From Cooley's series it is apparent that the higher the pulmonary vascular resistance is, the higher the surgical mortality rate. The ratio of pulmonary vascular resistance to total systemic resistance exceeded 0.2 in 34 patients who had a 38 per cent survival following operation. In 24 patients in whom this ratio was below 0.2, the survival rate was 87 per cent.[8] It is difficult to assess the effect of this variable independent of that of age because elevated pulmonary vascular resistance is normally present in the very young.

Systemic oxygen desaturation also has a profound influence on the surgical survival rate. Among 35 patients from Cooley's series who had a systemic arterial saturation of below 85 per cent, 46 per cent survived surgery. In 21 patients whose saturations exceeded 85 per cent there was a 86 per cent survival rate.

Additional factors which adversely influence outlook, either with or without operation, include small intra-atrial communications and relatively hypoplastic left heart chambers. Patients with obstruction to pulmonary venous return from whatever cause also do much more poorly than those in whom there is unimpeded flow back to the right atrium.

Discussion

The entity of TAPVR presents a broad spectrum in its clinical course. This is illustrated by the three cases presented in this paper. One patient presented as a critically ill infant who died in spite of surgical therapy. A second patient had surgery at age six years because of exercise intolerance and poor growth and development. The third patient is still living at the age of 46 years, having led a relatively normal life without surgical correction. It is unfortunate that patients similar to the latter two represent only a small fraction of those with TAPVR. The more usual situation is illustrated by the first patient.

The common dilemma, then, is the very young, very ill patient with congestive heart failure whose chances of survival with operation are poor and whose prognosis without operation is even worse. The literature pertaining to this entity would seem to indicate that operation should be performed promptly in such patients. On the contrary, it would seem that if the diagnosis is made during early life and the patient is not in congestive heart failure and is not severely ill, surgical treatment should be postponed until such an age when it can be done with a less prohibitive risk. The percentage of these less ill patients living to adulthood without operation does not seem large enough to justify an indefinite substitution of medical for surgical management. In almost all of these situations it seems that resorting to surgical therapy is choosing the lesser of two evils. It is obvious that the optimal timing of the operation is a crucial factor. It is preferable to wait until after one year of age when the surgical risk is less. However, often this is impossible and the acutely ill infant must be operated upon as a last resort when it is apparent that survival to a later, safer age is unlikely.

Careful angiographic and catheterization studies are important in making decisions regarding management of these patients. In addition to making the diagnosis there are several factors which should be determined. The assessment of the size of the interatrial defect is extremely important. The presence of a significant gradient between the two atria may signify a situation wherein the patient would benefit from a balloon septostomy which could palliate and postpone operation to a later and less risky age. The measurement of a pulmonary wedge pressure and its comparison with the right atrial pressure may indicate the presence of a pulmonary venous obstruction and thus point out the necessity of early operation. Good quality and expertly interpreted angiograms are invaluable in diagnosis and planning the surgical management of this disease.

It is through the continuing developments in cardiovascular surgery that many of these patients are now salvagable who would have previously had no chance for survival. It can only be hoped that similar future advances will help to further reduce the surgical mortality rates, especially during the early months of life.

Summary

Total anomalous pulmonary venous return (TAPVR) is a relatively uncommon congenital heart lesion which usually results in death during the first year of life. The spectrum of this disease is varied and does include an occasional patient who survives until adulthood. This spectrum is illustrated by three of the 27 cases of TAPVR seen at Colorado General Hospital who are reported herein. One of our patients is still alive at age 46 years and represents the oldest patient with this entity who has been reported in the literature. Cardiovascular surgical advances during the last fifteen years have made possible the correction of this previously untreatable lesion. The clinical, hemodynamic, and surgical aspects of TAPVR as observed in our patients are presented and compared with other series in the literature.

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Fundamentals of clinical cardiology

A reappraisal of concealed atrioventricular conduction

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Concealed atrioventricular (A-V) conduction is only recognized by its influence on the conduction or formation of the subsequent cardiac impulse. Two major features are observed in concealed conduction: (1) Disturbance of the conduction of the subsequent beat occurs when a new period of refractoriness is produced and (2) a subsidiary pacemaker (usually the A-V node), which is located within the conduction pathway of the basic impulses, is passively and prematurely discharged, leading to failure of impulse formation by the subsidiary pacemaker.

Although concealed conduction may occur anywhere in the heart, most frequently it occurs in the A-V junctional tissues. Concealed A-V conduction is defined as a deep penetration of the atrial impulse into the A-V junction without actual conduction to the ventricles. This deeply penetrated atrial impulse creates a new refractory period which influences the subsequent beat. Thus concealed A-V conduction is recognized by the following findings: (1) An unexpectedly long P-R interval or a blocked P wave is observed when the refractory phase of the A-V junction is expected to be over. (2) The A-V node fails to produce the expected escape beat following a long pause.

The concept of concealed A-V conduction had been studied as early as 1894 by Engelmann[1] and subsequently by Erlanger[2] in 1905. Later in 1925 extensive experimental investigation regarding the mechanism of concealed conduction was carried out by Ashman,[3] Lewis and Master,[4] and Drury.[5,6] These experimental studies were followed by clinical and electrocardiographic studies by various investigators.[7-13]

Since 1948, concealed A-V conduction has been extensively studied in clinical electrocardiology by Langendorf and Pick[8-13] and has become a distinct electrocardiographic entity. Recently, concealed conduction was further studied by Hoffman, Cranefield, and Stuckey[14] with the use of microelectrodes. They observed that concealed conduction occurred not only in the A-V junctional tissues but also in the right or left bundle branches and Purkinje fibers. The same authors proposed that decremental conduction may be responsible for many instances of concealed A-V conduction. Very recently, Moe and co-workers[15-17] studied the influence of concealed conduction both on the conduction of the subsequent impulse and on the discharge of the A-V nodal pacemaker, and they determined the duration of concealed conduction at varying driving rates. These authors also demonstrated that concealed A-V con-

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Fig. 1. Sinus rhythm with frequent ventricular premature contractions (V) and A-V nodal premature contraction (N). It is interesting to note the P-R interval following an interpolated ventricular or A-V nodal premature contraction is markedly prolonged. This phenomenon is due to concealed retrograde ventriculoatrial conduction.

duction is responsible for the irregular ventricular response in uncomplicated atrial fibrillation, although the same idea was described previously by Söderström.[1] Repetitive concealed conduction has been reported by different authors.[16-17]

Diagnostic criteria

Concealed A-V conduction is diagnosed[1-17] only by the recognition of indirect evidence supplied by the subsequent beat due to the deep but incomplete, penetration of the impulse into the A-V junctional tissues. Therefore the term concealed is used. The origin of a concealed impulse may be sinus or ectopic and the impulse may be conducted in an antegrade (forward) or retrograde fashion. Concealed A-V conduction is prone to occur at the transition between an absolute refractory period and the beginning of the recovery period. It is recognized by the unexpectedly long P-R interval or a blocked P wave and by the unexpected failure of the subsidiary pacemaker impulse to appear. The most common example of concealed A-V conduction is the full compensatory pause following a ventricular premature contraction and the prolonged P-R interval following an interpolated ventricular premature contraction. Another common example is the grossly irregular ventricular response seen in uncomplicated atrial fibrillation. Various forms of concealed A-V conduction are observed because of the development of a new refractory period created by the deep but incomplete, penetration of the impulse which influences the subsequent beat.

Influence on A-V (or V-A) conduction

INFLUENCE OF VENTRICULAR PREMATURE CONTRACTION. The most common occurrence of concealed A-V conduction is the full compensatory pause following an ordinary ventricular premature contraction (extrasystole) and the long P-R interval following an interpolated ventricular premature contraction (Fig. 1). A long pause following a ventricular premature contraction is also often observed in the presence of atrial fibrillation and this is analogous to the full compensatory pause in sinus rhythm.

These electrocardiographic changes occur because the deep penetration of a retrograde ventriculoatrial (V-A) impulse originating from a ventricular ectopic focus creates a new refractory period in the A-V junction which influences the subsequent beat. For the same reason, a longer P-R interval or an unexpectedly blocked P wave in atrial tachycardia or an unexpectedly blocked flutter wave in atrial flutter may be observed following a ventricular premature contraction due to concealed V-A conduction.

In addition concealed V-A conduction from a ventricular premature contraction may produce an unexpectedly long P-R

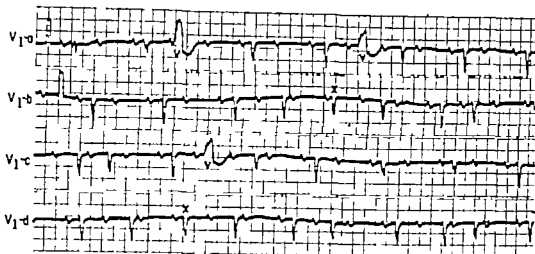


Fig. 2. Lead V_1 (*a*, *b*, *c* and *d* are continuous). This tracing shows second degree A-V block consisting of 2:1 and Wenckebach A-V block and ventricular premature contractions (V). It is interesting to note that A-V conduction is altered (either unexpectedly blocked P wave or markedly prolonged P-R interval) following ventricular premature contractions (V) due to concealed retrograde ventriculoatrial conduction. In addition some P waves (eighth P wave of Lead V_1 [*b* strip] and third P wave of Lead V_1 [*d* strip]) instead of being blocked during a Wenckebach period are conducted to the ventricles (X) with extremely prolonged P-R intervals (0.68 to 0.80 second) which are longer than the P-P intervals (0.62 second). As a result, P waves immediately preceding QRS complexes marked X are blocked. Therefore two P waves exist between the R-R intervals, the first conducted, the second blocked. This phenomenon has been called skipped P wave.

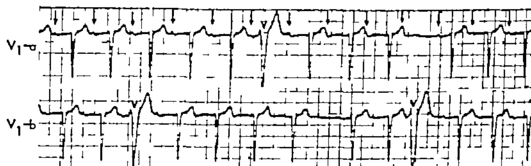


Fig. 3. Lead V_1 (*a* and *b* are continuous): arrows indicate P waves. The tracing shows sinus rhythm with Wenckebach A-V block and ventricular premature contractions (marked V). Note alteration of the P-R interval following a ventricular premature contraction due to concealed retrograde ventriculoatrial conduction.

interval or a blocked P wave subsequently in the presence of second or high degree A-V block. For instance, the P-R interval of the conducted beat following the ventricular premature contraction in 2:1 A-V block will be longer than those of the remaining conducted beats when concealed V-A conduction occurs in the former (Fig. 2). Another example is that the typical feature of Wenckebach A-V block may be altered because of concealed V-A conduction from a ventricular premature contraction. That is, the P-R interval after the pause (dropped P wave) in Wenckebach A-V block is longer than expected when a ventricular premature contraction occurs just before the appearance of the first conducted beat after the pause (Fig. 3).

Furthermore, concealed V-A conduction from a ventricular premature contraction in the presence of second or high degree A-V block may increase the degree of A-V block. In this case, 2:1 A-V block may become 3:1 A-V block, or 3:1 A-V block may become 4:1 A-V block because of the unexpected additional blocked P wave (Figs. 2 and 4).

INFLUENCE OF A-V NODAL OR ATRIAL PREMATURE CONTRACTION. Less commonly, an A-V nodal premature contraction may influence A-V conduction so that concealed A-V conduction occurs. This may occur in sinus or ectopic rhythm. It is not uncommon to observe a long P-R interval following an interpolated A-V nodal premature contraction (Fig. 1), as seen in interpolated

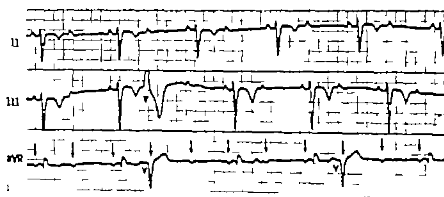


Fig. 4 Arrows indicate P waves. The tracing reveals sinus rhythm with 2:1 A-V block and ventricular premature contractions (V). Note that 3:1 A-V block is produced following ventricular premature contraction (V) resulting from concealed retrograde ventriculoatrial conduction.

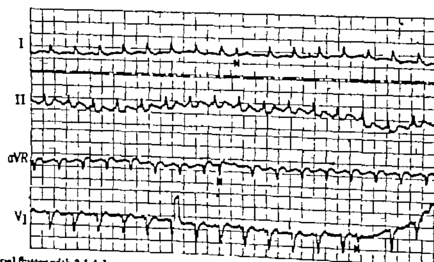


Fig. 5 Atrial flutter with 2:1 A-V response and A-V nodal premature contractions (N). Note a long pause following the A-V nodal premature contraction due to concealed A-V conduction.

ventricular premature contraction. Concealed conduction is apt to occur when the underlying rhythm has a rapid rate. For example, atrial flutter with 2:1 A-V response may become 3:1 or 4:1 A-V response following an A-V nodal premature contraction because of concealed A-V conduction (Fig. 5).

On rare occasions, A-V conduction becomes delayed following an atrial premature contraction when concealed A-V conduction occurs. This is particularly true following an apparently blocked (nonconducted) atrial premature contraction even though the returning cycle (the interval from ectopic P wave to the P wave of the subsequent sinus beat) may be long (Fig. 6). Concealed A-V conduction occurs in this circumstance when the ectopic atrial impulse transmits very slowly but deeply, creating a new refractory period in the A-V junction. It has been shown that the slower the speed of concealed conduction, the more marked is the influence on the conduction of the subsequent beat, regardless of the ultimate extent of the penetration of the impulse.

ALTERATION OF A-V CONDUCTION IN A-V BLOCK. Concealed A-V conduction influences A-V conduction in pre-existing second or high degree A-V block. The former is manifested by an unexpectedly long P-R interval in the subsequently conducted beat compared with those of the remaining conducted beats, or an additional unexpectedly blocked P wave. For exampl

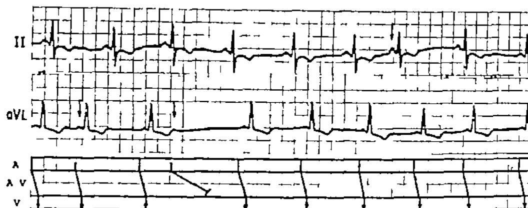


Fig. 6. Sinus rhythm with atrial premature contractions (indicated by arrows). It is interesting to observe that the P R interval of the sinus beat following nonconducted atrial premature contraction is longer than other sinus beats. This finding is most likely due to concealed A V conduction.



Fig. 7. Lead II (a and b are continuous strips taken during an acute diaphragmatic myocardial infarction) arrows indicate P waves. The tracing reveals a mixture of 2 1 A V block and Wenckebach period. It is interesting to note that the P R interval (X) following a blocked P wave is unexpectedly long. The reason for this is that an atrial impulse which fails to reach the ventricles, actually penetrates deeply into the A V junction so that a new refractory period is created. Consequently the subsequent atrial impulse is conducted to the ventricles slower than usual (concealed A V conduction).

the P R interval of the conducted beat in 2 1 A V block may be longer than expected without changing the A V ratio when concealed A V conduction occurs in the preceding atrial impulse (Fig. 7). On the other hand concealed A V conduction may produce an unexpectedly blocked P wave on the subsequent beat when a new absolute refractory period is created in the A V junction. For instance 2 1 A V block may become 3 1 or 4 1 A V block because of concealed A V conduction in the preceding atrial impulses. The increased A V ratio found in second or high degree A V block which results from concealed V A conduction of a ventricular premature contraction was described previously. Three to one A V block is often a variant of 3 2 A V block (either Mobitz Type I or II) resulting from concealed A V conduction (Fig. 8).

ALTERATION OF A V CONDUCTION IN ATRIAL TACHYARRHYTHMIAS. One of the most common occurrences of concealed A V conduction is found in uncomplicated atrial fibrillation. The grossly irregular ventricular rhythm in atrial fibrillation indicates alteration of the refractory period in the A V junctional tissues from beat to beat. This varying ventricular response is considered to be due to varying degrees of incomplete penetration of the atrial fibrillation impulses into the A V junction (concealed A V conduction) which influences the transmission of the subsequent impulses. Otherwise the ventricular rhythm in uncomplicated atrial fibrillation would be regular because the atrial impulses are always available for transmission to the ventricles whenever the A V junction is in the nonrefractory period.

Evidence for concealed A V (or V A) conduction in atrial fibrillation is provided by the following (1) an irregularly irregular ventricular rhythm in uncomplicated atrial fibrillation (2) the occurrence of a post

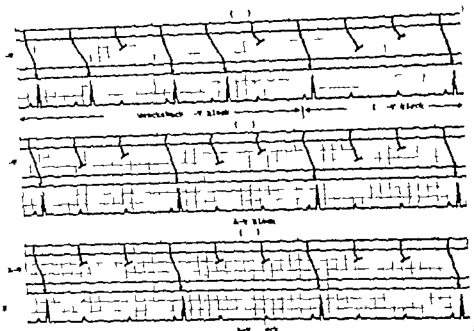


Fig. 8. This diagram illustrates various mechanisms responsible for the production of 3:1 A-V block. *A*, 3:2 Wenckebach A-V block followed by an area of 3:1 A-V block. During 3:1 A-V block, two blocked atrial impulses actually penetrate into the A-V junction but fail to reach the ventricles. The first blocked atrial impulse penetrates deeply into the A-V junction so that a new refractory period is created in the A-V junction (concealed A-V conduction). Thus, the subsequent atrial impulse is blocked. From this observation, 3:1 A-V block may be a variant of 3:2 Wenckebach A-V block due to concealed A-V conduction. *B*, 3:1 A-V block due to 3:2 Mobitz Type II A-V block with concealed A-V conduction. In this case, two successive atrial impulses are blocked but the first atrial impulse penetrates deeply into the A-V junction to create the new refractory period. Thus, subsequent atrial impulses are blocked due to concealed A-V conduction. From this observation, 3:1 A-V block may be a variant of 3:2 Mobitz Type II A-V block. *C*, 3:1 A-V block due to two successive blocked atrial impulses with equal penetration into the A-V junction.

ectopic pause following a ventricular premature contraction analogous to the full compensatory pause during sinus rhythm; (3) an unexpectedly longer escape interval because the A-V nodal pacemaker fails to produce an escape impulse at the expected time when the A-V node is passively discharged by the concealed atrial impulse (Fig. 9); (4) enhancement of the ventricular rate resulting from the elimination of concealed conduction when atrial fibrillation changes to atrial flutter; (5) the occurrence of two or more successive long ventricular cycles in uncomplicated atrial fibrillation due to repetitive concealed A-V conduction. When repetitive concealed A-V conduction occurs in atrial fibrillation, a long ventricular standstill may result.

It is known that the A-V conduction ratio in atrial flutter or tachycardia may alter when concealed A-V conduction occurs. For example, in most instances, atrial flutter with 3:1 or 4:1 A-V block is attributed to concealed A-V conduction of varying degrees. A-V block of varying degree which is due to concealed A-V conduction in the presence of atrial flutter may be manifested by Mobitz Type I or II A-V block. In addition, an unexpectedly long P-R interval or a blocked P wave may occur in atrial tachycardia when concealed A-V conduction occurs (Figs. 10 and 11).

RELATIONSHIP TO SUPERNORMAL A-V CONDUCTION. In rare instances, the occurrence of supernormal A-V conduction is observed to be closely related to concealed A-V conduction. Supernormal A-V conduction has been discussed in detail previously.[13]

Influence on the impulse formation of the subsidiary pacemaker

HIGH DEGREE (ADVANCED) A-V BLOCK WITHOUT SUBSIDIARY PACEMAKING MECHANISM. In high degree A-V block concealed

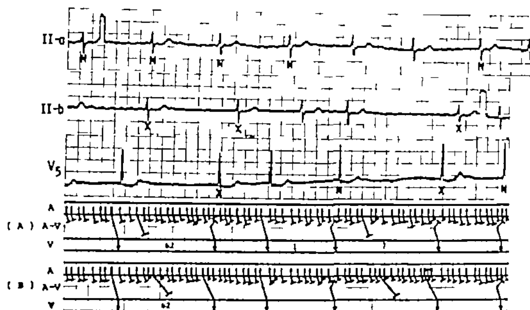


Fig. 9. Lead II (*a* and *b* are continuous). The rhythm is atrial fibrillation with intermittent A-V nodal escape rhythm (N; rate, 52 beats per minute) and areas of unusually long ventricular pauses (X). These ventricular pauses vary considerably in their duration and do not have any relationship to the escape intervals. The ventricular pause can be explained on the basis of concealed A-V conduction. Namely, the A-V nodal pacemaker is prematurely and passively discharged by a deeply penetrated atrial impulse in the A-V junction so that a new set of A-V nodal escape intervals is produced (diagram *A*). On the other hand, the ventricular pause may be due to consecutively appearing blocked atrial impulses resulting from a deeply penetrated atrial impulse which produces a new refractory period in the A-V junction (diagram *B*). These phenomena are manifestations of concealed A-V conduction. (The numbers represent hundredths of a second.)

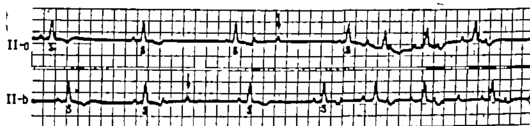


Fig. 10. Lead II (*a* and *b* are continuous). The tracing shows sinus bradycardia (38 beats per minute) and paroxysmal atrial tachycardia (150 beats per minute) with varying A-V block. A nonconducted ectopic P wave (indicated by arrow) is considered to be due to concealed A-V conduction of the preceding beat.

A-V conduction is usually considered to be responsible when an A-V nodal escape beat fails to appear in spite of a slow ventricular rate. Concealed A-V conduction is manifested in this case by a failure of the A-V node to escape because the A-V node is passively discharged by a deeply penetrating atrial impulse (Fig. 9).

VENTRICULAR ESCAPE BEATS IN SECOND OR HIGH DEGREE A-V BLOCK. When the ventricular rate is slower than 55 beats per minute in second or high degree A-V block, one or more A-V nodal escape beats occur to control ventricular activity. However, on rare occasions the A-V node fails to produce an escape impulse in spite of the slow ventricular rate and instead a ventricular escape beat may occur. Failure of the A-V node to produce an escape impulse in this case is often attributed to the passive discharge of the A-V node by the concealed A-V conduction of the preceding atrial impulse (Fig. 9). However, it should be noted that significant damage to the A-V node itself may also be responsible for a failure of the A-V node to produce an impulse.

ALTERATION OF THE A-V NODAL ESCAPE INTERVALS. The A-V nodal escape intervals are usually regular in most instances, but they may become irregular when concealed A-V conduction occurs in incomplete A-V

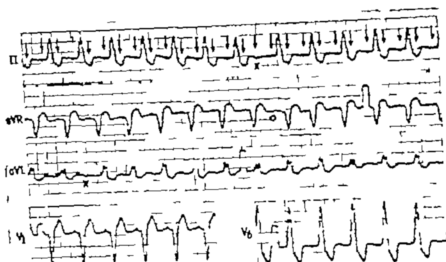


Fig. 11 Arrows indicate P waves. The rhythm is atrial tachycardia (most likely left atrial in origin) with 2:1 A-V response (atrial rate, 185 beats per minute). It is interesting to note that the P R interval is occasionally prolonged in conducted beat (O) and some P waves are unexpectedly blocked (X). These findings are most likely due to concealed A-V conduction.



Fig. 12 Arrows indicate P waves. The rhythm is marked sinus bradycardia (atrial rate, 33 beats per minute) with intermittent A-V nodal escape rhythm (A rate, 42 beats per minute) producing incomplete A-V dissociation. Note that the A-V nodal escape interval *following* blocked P wave is occasionally longer than others. This is most likely due to concealed A-V conduction. S indicates conducted sinus beat (ventricular captured beat). (The numbers represent hundredths of a second.)

dissociation. For example an A V nodal escape beat occurs later than in the usual cycle in incomplete A V dissociation when the atrial impulse of the preceding beat penetrates deeply into the A V junction (concealed ventricular captured beat) so that A V nodal impulse formation is delayed due to a newly formed refractory period in the A V junction (Fig 12). In this circumstance when the underlying rhythm is atrial fibrillation it is difficult to be certain whether the unexpectedly long R R interval is due to a delayed A V nodal escape beat or to a failure of the A V nodal pacemaker to produce an impulse, leading to the delayed occurrence of a conducted atrial fibrillation beat (Fig 9). In addition the A V nodal escape interval may be longer than expected because of a delayed impulse formation in the A V node resulting from retrograde concealed V A conduction of the preceding A V nodal beat.

VENTRICULAR STANDSTILL. One of the important causes of ventricular standstill is considered to be repetitive concealed A V conduction. Ventricular standstill may occur when concealed A V conduction occurs on successive beats because of the newly created long refractory period in the A V junction. In this case, the A V node is unable to produce an escape impulse on succession in spite of a slow ventricular rate as the A V node is passively discharged by the deeply penetrating atrial impulses (Fig 9).

Clinical significance

Concealed conduction may occur at any location in the heart but the most common area is in the A V junctional tissues. The

rare occurrence of a concealed extrasystole was reported[22] but concealed intraventricular conduction is not uncommon[10-13] Concealed A V conduction may be observed in a normal as well as an abnormal heart but it tends to occur much more frequently in the heart with impaired A V conduction

The recognition of concealed A V conduction is essential to understand various simple and complex cardiac arrhythmias. An unexpectedly long P R interval or a blocked P wave or the unexpected failure of the A V node to produce an escape impulse is often due to concealed A V conduction In a practical sense almost all of the complex arrhythmias may be related to some form of concealed conduction

Concealed A V conduction itself does not produce any symptoms or signs but an unexpectedly slow ventricular rate or ventricular standstill resulting from concealed A V conduction certainly may produce Adams-Stokes syndrome and/or congestive heart failure Thus the treatment and prognosis depend upon the consequence of the concealed A V conduction in addition to the underlying heart disease Concealed A V conduction is frequently observed in digitalis intoxication since the complex arrhythmias are often produced by the former as well as the latter[23]

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Julian Frieden

The influence of heart failure, liver disease, and renal failure on the disposition of lidocaine in man

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The extensive use of lidocaine as an intravenous antiarrhythmic drug has led to a large clinical experience with therapeutic responses and adverse effects. As with other drugs, there is a growing awareness that disturbed function of organ systems which distribute, metabolize, and excrete the agent may alter sensitivity to the therapeutic and toxic effects of the drug. When systemic and regional circulation is altered, as in severe heart failure, then distribution of the agent carried in the blood may similarly be altered. In several species of mammals tested and probably also in man, most of injected lidocaine is metabolized in the liver. With hepatic disease, metabolism of the agent may be impaired and the rate of metabolism slowed. A weak base, the renal clearance of lidocaine is influenced by urinary pH. Its excretion into alkaline urine is negligible. In a group of our patients in whom no attempt was made to control the pH of the urine, less than 5 per cent of the administered dose appeared in the urine as unchanged drug. Into maximally acid urine, the clearance of lidocaine increases and slightly exceeds simultaneously measured inulin clearances. However, even at this maximal rate, renal clearance of lidocaine accounts for no more than 20 per cent of the total body clearance of the agent.[1] It is not anticipated that the presence of renal disease would severely alter the individual's ability to distribute or remove the drug from the body.

In the settings of the Coronary Care Unit where lidocaine is used so extensively, many patients in addition to their cardiac arrhythmias may evidence heart failure, liver disease, and/or renal failure. Reports of increased sensitivity to the toxic effects of lidocaine in patients with heart failure and liver disease[2,3] were confirmed by our own observation and led us to undertake studies to examine the effects of these disease states on the disposition kinetics of lidocaine. A group of subjects with renal disease were also studied.

The heart failure subjects all had elevated ventricular filling pressures and a low cardiac index as well as clinical signs of heart failure. The group included patients with coronary artery disease, valvular heart disease, and myocardiopathy. All patients with liver disease were alcoholic and each

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had been hospitalized for treatment of hepatic decompensation All had clinical stigmas of advanced liver disease and liver function tests consistent with alcoholic cirrhosis. The patients with renal disease were on chronic dialyses between studies Five were anephric and the remaining two were oliguric producing less than 100 c c. of urine per day The results of these studies are reported in detail elsewhere[4] and summarized in the following discussion

Calculation of kinetic terms

Following the administration of a 50 mg intravenous dose of lidocaine plasma levels were measured and the data were fitted by nonlinear regression analysis on a digital computer to a biphasic curve as shown in Fig 1 The kinetic terms measured include the volume of distribution (Vd) the plasma half life of the slower phase of the curve ($T1/2$) and the plasma clearance (C) Vd $T1/2$ and C are defined in the following equations

$$Vd = \frac{D}{B} \quad (1)$$

$$T\,1/2 = \frac{0.693}{\beta} \quad (2)$$

$$C = \frac{D}{\text{area under the curve}} = \frac{D}{\frac{A}{\alpha} + \frac{B}{\beta}} \quad (3)$$

D is the dose of lidocaine A and B are the zero time intercepts of data plotted on semilogarithmic paper α and β are the rapid and slow constants respectively[5]

Knowledge of C in a given patient permits prediction of steady state plasma concentration during a continuous infusion by the formula

$$P = \frac{S}{C}$$

where P is the plasma concentration of lidocaine and S is the rate of constant infusion

Results

The results of these studies are summarized in Table I In all groups Vd exceeded any real volume or body compartment, indicating that after the rapid distribution phase (α) the plasma concentration of lido-

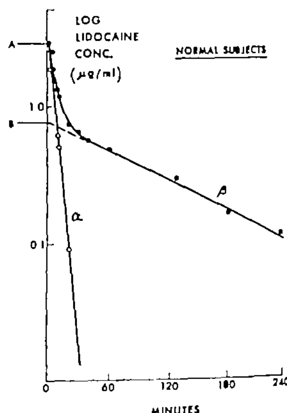


Fig 1 A biexponential curve following a single intravenous bolus of 50 mg of lidocaine.

caine is low and that the drug is rapidly taken up from the plasma by the tissues. It is of interest to note that a significant reduction in Vd is seen only in heart failure patients. Blood levels in this group were higher throughout the period of observation (Fig 2) Plasma clearance of lidocaine was significantly reduced in both heart failure and liver disease subjects

The importance of a reduced Vd and C is graphically illustrated in Fig 3 In the normal subject Vd and C had been previously determined and were used to calculate amounts of lidocaine in an intravenous bolus followed by a constant intravenous infusion which would rapidly obtain and then sustain a plasma level of 1 µg per milliliter* In the heart failure subject of similar weight a minimal therapeutic dose was administered with a 50 mg bolus followed by a 1 mg per minute infusion Published estimates of the plasma concentrations which correlate with central ner

*The formulas for these computations were:

$$I = Vd \times P \quad (1)$$

and

$$S = C \times P \quad (2)$$

I is the amount of lidocaine in the initial bolus expressed in micrograms.

vous system toxicity range from 5 to 7 μg per milliliter.[4-6] Note in Fig. 3 that within two hours the concentrations of lidocaine approached toxic values in this subject with advanced heart failure even though the infusion rate was near the minimum recommended dose. Although this may be an unusual instance of drug accumulation, the easy ability to reach toxic concentrations of the drug in some patients illustrates the need for caution and preset objectives for toxicity in all patients. Had this infusion been continued until a steady state had been achieved, we estimate that the blood level would approach 12 μg per milliliter.

The volume of distribution in the liver disease subjects did not differ from the normal, but the clearance was reduced and the half life prolonged. No significant reduction in the volume of distribution or clearance was observed in patients with renal disease.

Discussion

The recommended infusion rates for lidocaine suggested by Gianelli and associates and now recommended in the package inserts of lidocaine (Xylocaine*) range from a minimum of 20 to a maximum of 50 μg per kilogram per minute. At the maximum rate, we estimate that the majority of the heart failure and liver disease subjects studied would achieve steady state plasma concentrations in excess of 5.5 μg per milliliter. These data suggest that clinical assessment of the status of cardiovascular and hepatic function are important considerations in selecting a therapeutic dose of lidocaine and that all patients receiving the drug require observation for adverse effects, even if doses are within the currently recommended ranges.

From the previous considerations of metabolism and excretion it is not surprising that liver failure patients have a reduced plasma clearance of lidocaine and that renal failure patients do not significantly differ from normal in any of the derived kinetic parameters. In heart failure patients the profound reduction of clearance and the significant reduction in volume of

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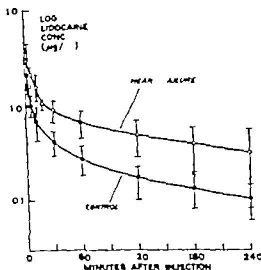


Fig. 2. Arithmetic mean values ± 1 S.D. for plasma concentrations of lidocaine in 7 heart failure subjects following a 50 mg. intravenous bolus, illustrating that plasma concentrations in heart failure subjects were elevated throughout the period of observation.

distribution suggest that the drug is being taken up from plasma at a reduced rate. This may result from changes in total blood flow and/or distribution of the circulation, both of which are known to accompany heart failure. A reduced perfusion of tissue beds which normally take up large amounts of the agent may result, and the total number of tissues competing for the drug may be reduced by this mechanism. Similarly, reductions in hepatic and splanchnic blood flow with heart failure may result in a decreased rate of delivery of the agent to the liver, effecting a slower delivery of agent to the site where it is metabolized and accounting for the decreased clearance. An impaired capacity of the liver to metabolize the agent once it has been delivered might also result from decreased hepatic blood flow and/or venous congestion.

If redistribution of the circulation is a mechanism by which higher blood levels are produced for a given dose, it is of interest to note that the redistribution of blood flow accompanying heart failure tends to favor flow to the heart and brain. Preserved flow of blood containing increased concentration of the drug may result in increased accumulation of the drug in these organs. It is precisely these

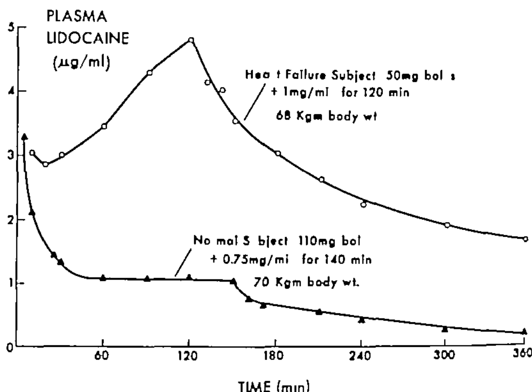


Fig 3 Illustration of the difference in plasma level response to infused lidocaine in a normal subject and a heart failure subject of similar size

Table I Metabolism of lidocaine

Group of patients	*Volume of distribution (L/Kg)*	*Plasma half-time (min)*	*Plasma clearance (ml/min)*	*Plasma clearance (ml/min/Kg)*
Normal (N = 10)	1.70 ± 0.21	108 ± 7	701 ± 41	9.2 ± 0.8
Heart failure (N = 7)	1.01 ± 0.27 (<0.05)	136 ± 35 (NS)	358 ± 147 (<0.05)	5.0 ± 2.5 (<0.05)
Liver disease (N = 8)	2.22 ± 0.94 (NS)	343 ± 234 (—)	368 ± 180 (<0.05)	5.2 ± 2.1 (<0.05)
Renal disease (N = 7)	1.82 ± 0.34 (NS)	115 ± 49 (NS)	692 ± 136 (NS)	11.3 ± 2.0 (NS)

*NS = Not significant.

organs which are most sensitive to the toxic effects of lidocaine which may in turn account for the increased sensitivity to the toxic effects of lidocaine seen in heart failure subjects.

Following intravenous administration the plasma time concentration curves of many drugs assume a biexponential curve similar to that shown for lidocaine in Fig 1 The early rapid phase (α) is referred to as the distribution phase and reflects a rapid distribution of the drug to the body tissues. This phase merges with a slower phase (β) which reflects a constant fractional rate of metabolism and excretion of the drug The slower phase assumed clinical importance in predicting when a given rate of administration of the agent will produce a constant blood level Plasma levels will increase during a constant rate of infusion and the plasma levels will reach within 90 per cent of the plateau after a period of approximately 3 half lives ($T1/2\beta$) The 3 times rule also applies to upward and downward changes in existing infusion rates.[9] A period of approximately five times the half life is required before a given adjustment in infusion rate will produce a new constant plasma level

With the growing clinical use of plasma concentrations of drugs to assist in decisions whether or not to administer more or less of the agent, recognition of this time lag between when a dosage changes and

when the effect of that change is maximal is essential to proper interpretation of a plasma level Knowledge of the half-life of the drug in normal subjects cannot be generalized to all patients. The period of time required for the blood level to plateau following a change in a dosage regimen in our normal subjects ranges from 6 to 10 hours. In our liver disease subjects the range was 9 to 58 hours. Recogn tion of this difference permits the physician to approach the liver disease patient with a different level of expectation than the patient who is free of liver disease.

Conclusion

In patients requiring intravenous lidocaine for control of arrhythmias, coexisting heart failure and/or liver disease are likely to result in a decreased dose requirement. Failure to recognize this is likely to result in unnecessary toxicity and increased pa tient morbidity Even in normal subjects and patients with renal failure, existing dosage recommendations may on occasion place blood levels within the toxic range pointing to the need for close observation of all patients receiving this drug Appreciation of the dominant phase" half-life perm ts a clinical estimate of when a given rate of administration is likely to produce ts full effect. This time lag between dosage change and eventual plateau concentration may be markedly prolonged in most patients with advanced alcoholic cirrhosis.

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Annotations

The management of deep vein thrombosis

Deep vein thrombosis of the lower limbs and its consequences constitute an important clinical problem which has not yet been satisfactorily resolved. Pulmonary embolism is now one of the commonest causes of death after surgery[1] not only is this relatively frequent in prostrating medical illness[2] but it is also the greatest single factor in maternal deaths in childbirth. Apart from the immediate risk to life, there are the late sequelae, following destruction of venous valves, of swelling of the legs, varicose veins, varicose eczema and ulceration and other trophic changes, representing some of the commonest and most intractable problems in surgery.

In the past a crucial difficulty in the management of deep vein thrombosis has been the lack of means for the recognition of this condition, particularly in the early stages. If one relies solely on clinical signs there will be failure to diagnose the condition in 50 per cent of patients.[7] Some of the more modern developments in phlebography are undoubtedly accurate in demonstrating thrombosis[4] but are not suitable as a routine method for screening large numbers of patients. Ultrasound techniques are relatively simple but are limited in their use. In the absence of sensitive and accurate techniques for diagnosing this condition, it has not been possible to study the natural history of the thrombotic process, whether it is spreading, remaining stationary or lysing. No means were available for measuring with any precision the effects of prophylaxis or treatment of the condition.

Within the last two years many of these difficulties have been overcome. A sensitive technique, using ^{125}I labelled fibrinogen has been developed and has now been widely used. This test depends on the fact that radioactive fibrinogen circulating in the bloodstream is incorporated into a forming clot, and the increased radioactivity over the clot can be detected by an external counter.[4] The accuracy of this test in diagnosing deep vein thrombosis has been confirmed by phlebography.

The radioactive fibrinogen test has now been used to study the true incidence of deep vein thrombosis in surgical, medical, and obstetric patients. The details of this test have been described elsewhere.[4] Briefly, in surgical patients, the thyroid gland is blocked by sodium iodide (100 mg) in order to prevent excessive uptake of radioactive iodine; this is given orally 24 hours before the intravenous injection of 100 µc of ^{125}I labelled fibrinogen on the day before operation. In postpartum patients, sodium iodide can be given intravenously immediately after delivery and half an hour later ^{125}I labelled fibrinogen is injected. A similar procedure can be adopted for medical patients. The radioactivity over the limbs is then measured one hour later and again on subsequent days. The older method of counting radioactivity where absolute counts were obtained at each position in the limb has now been superseded by a much simpler and quicker technique, using a ratemeter.[9] Human fibrinogen is used and the preparation of this material to avoid the risk of serum hepatitis is described in detail elsewhere. This material has been used in over 400 patients and no case of serum hepatitis has occurred and no difficulty encountered with the labelling process.

It has been shown that in surgical patients aged 40 and over there is a 35 per cent incidence of thrombosis following operation. In older patients (above 60) undergoing major operations, there is an even greater incidence of over 60 per cent.[11] In half of these patients, the thrombosis commences on the operating table. The clot almost always starts in the soleal sinuses and tibial veins in the calf and, in most cases, spontaneous lysis occurs within a few days. In only 25 per cent does the process extend from the calf more proximally into the popliteal, femoral and iliac veins.[11] In this group with extending thrombosis, pulmonary embolism occurs in almost 50 per cent of the patients. Although the emboli are often of a minor nature, nevertheless, they serve as a warning of the potential danger to life. In contrast, where the thrombus is confined to the calf embolism does not occur[11] and is never present when the radioactive test is negative.

In prostrating medical illness, such as myocardial infarction, there is an incidence of deep vein thrombosis in the region of 40 per cent.[12] In contrast, in postpartum women the incidence is very much lower, about 5 per cent.[6] It is not clear whether this reduced incidence is associated with a younger age or some other factor in pregnancy.

There are certain defects of the radioactive fibrinogen test. Diagnosis of a thrombus depends upon a sufficient difference between the radioactivity in the thrombus and in its surrounding background. In the upper thigh and pelvis, the proximity of large arteries and other factors give increased counts and make the test unreliable in these areas. Essentially the radioactive fibrinogen test should be used while a clot is forming. If the clot is stationary or dissolving, then the fibrinogen is not incorporated and there is no increased radioactivity. It is, therefore, less likely to be useful in late or established thrombosis.

The ideal t which to aim is the prevention of deep vein thrombosis. It is arguable whether the conventional measures used at present do in fact reduce the incidence of this condition some workers say they are of value[8] while others deny this. Unfortunately these conclusions are based on physical signs alone which are quite inadequate for diagnosing the presence of venous thrombosis. When the radioactive fibrinogen test has been used to diagnose thrombosis, it has shown that the conventional prophylactic measures employed in most hospitals are of limited value.[10] Even more intensive measures before, during, and after operation (including vigorous exercises and elastic stockings) are unable to reduce the incidence of postoperative deep vein thrombosis, except in elderly patients undergoing major surgery.[10] The use of oral anticoagulants before operation has also proved ineffective as prophylaxis.[8] Similarly disappointing results have been seen in patients receiving dextran infusion before and after surgery.[11] U til reliable methods of prevention are developed, the emphasis must be on promising modes of treatment, if morbidity and mortality rates are to be reduced.

Since the available forms of treatment are not always saf and not invariably effective, it is wise to restrict their use t selected patients. The natural history of deep vein thrombosis indicates clearly that patients with spreading thrombosis, involving the popliteal or even more proximal veins, require active treatment for at least two reasons first, there is significant risk of pulmonary embolism[11] and, second, as more extensive segments of the veins become involved, there is an increasing risk of the late sequelae of the postphlebitic syndrome.

There is still great deal of controversy as to which is the best form of medical treatment for patients with deep vein thrombosis. There have indeed been very few reported studies of treatment in homogeneous groups of patients where the effect of treatment has been measured by such objective means as the radioactive fibrinogen test and phlebography I one study the results of treatment were compared in three homogeneous groups of patients who were allocated at random to one of three treatment schedules.[17] One group received continuous heparin infusion for period of seven days; the second group was treated with the plasminogen activator streptokinase, which is known to have thrombolytic effect,[14,15] and the third group was given Arvin which has specific coagulant action on fibrinogen.[16] The results showed that there was little to choose between heparin and Arvin so far as their anticoagulant potential was concerned, except that the risk of hemorrhage appeared to be greater when heparin was used. Streptokinase was undoubtedly the most effective drug to use for lysing established thrombi, but it had certain disadvantages and was not uniformly successful. Factors known to affect its action are the extent and age of the thrombus. Since the activator must reach the thrombus to produce the desired effect, thrombolysis is achieved more readily in vessel which is not completely occluded. The age of the thrombus is also important because the best results are obtained if treatment is begun ithin 36 to 48 hours of onset.

When deep vein thrombosis has occurred, it seems likely that prevention of the late sequelae can best be brought about by the rapid and complete dissolution of thrombus with preservation of valvular function. What are the critical factors involved in the preservation of the function of venous valves I studies using ascending f nctional cinephlebography it has been clearly shown that early diagnosis is of paramount importance. This is only possible by routine use of methods such as the [125]I-labelled fibrinogen test.

In the absence of effective prophylaxis, the ideal is to screen all patients over the age of 40 undergoing surgery or confined to bed with prostrating medical illness. For this to be practical procedure, the technique of the [125]I-labelled fibrinogen test must be simple and quick. The recent introduction of the ratemeter[3] goes long way toward fulfilling these requirements. A technician or physiotherapist can scan the legs for the presence of deep vein thrombosis in few minutes. I this way the course of the thrombus can be followed, whether it is extending into the popliteal or more proximal veins, and appropriate treatment can then be instituted t the right time.

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A critique of the cardiac index

The introduction of surface area into hemodynamic indices probably occurred in 1918 when a significant statistical correlation was observed to exist between basal volume output per minute of the heart and basal rate of oxygen consumption Since basal rate of metabolism seemed to be related to the surface area of the body it was considered that cardiac output (CO) in man should also be related to his surface area The expression of CO per unit of body surface area was called the *cardiac index* (CI)

$$CI = \frac{CO\ (1/min.)}{body\ surface\ area\ (sq\ M)}$$

Since its introduction as a means of expressing CO the cardiac index (CI) has been a commonly employed physiologic unit. However we have wondered for many years why this unit is so commonly employed because, regardless of the reasons given, it has been obvious from its introduction that it could introduce a large unknown error in calculations. The large unknown error in CI stems from at least the imperfect methods used for calculating body surface area

Body surface area is obtained from a formula introduced by DuBois and DuBois[3] based on the subject height and weight. The accuracy of their formula was based on measurements of the surface areas of nine subjects obtained by making body molds of inflexible paper However areas such as the nose, ears and gluteal folds, scrotal area, and other intertriginous surfaces were grouped in an arbitrary fashion and not even measured In most subjects, only one leg and arm were measured. The areas of the hands were measured by making paraffin casts over cotton gloves. Following these measurements a formula based on height and weight was obtained by mathematical manipulation, to "fit the data from the nine subjects. From previous experience with measuring accurately the surface area of only the pinna of the ear and the finger and toe tips,[4] an error of at least ±10 per cent would seem likely in the estimation of total body surface area when calculated from height and weight as described by DuBois and DuBois.[3]

Thus, under present circumstances, the arbitrary use of surface area to express physiologic data in an effort to reduce the data to a common unit can introduce a large error For most purposes expression of CO as cardiac index is not even necessary nor desirable. If an accurate and reliable method for estimating surface area of the body existed, a measurement such as the CI might be acceptable. However until such a method is available it is more accurate to express data such as CO as a function of units that can be accurately measured, e.g body weight or per individual.

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Factors relating to the progression of diabetic retinopathy

The natural history of simple or exudative diabetic retinopathy is now well documented[1,2] and the fundamental pathological change of capillary leakage from microangiopathic foci established from fluorescein studies. In proliferative diabetic retinopathy the progressive nature of the phenomenon and the interrelationship between new vessel formation, connective tissue formation, and posterior vitreous face detachment are stressed. The nature of the factors which govern these processes is open to some discussion.

Although the prevalence of retinopathy in diabetics may be related to blood sugar levels, to duration of diabetes,[2,4] and to increasing age at diagnosis, it is less certain that these factors have any effect upon the natural history of established retinopathy. In a retrospective study by Caird and his co-workers and in a prospective study by Schlesinger and others,[10] no relationship was found between progression of established retinopathy and glycosuria. In contrast, Miki and colleagues[11] found more rapid progression of established retinopathy in patients with high blood sugar levels. These conflicting findings may result from the difficulty in accurate assessment of diabetic retinopathy with the use of descriptive methods alone.

A prospective study was recently carried out by Adnitt and Taylor[12] using serial fundal photography. The period of observation in 21 patients ranged from 30 to 103 months, with a mean of 50 months. The retinopathy in 37 eyes was assessed at the beginning and end of the period of observation by the Airlie classification.[13] This method compares the separate features of retinopathy with standard photographs. Background retinopathy, new disc vessels, new retinal vessels, fibrous tissue, and hemorrhages were evaluated separately and a total score obtained for each fundus. The difference between the score at the initial and final visits was taken as an index of progression. An annual index of progression was derived by dividing by the number of months of observation and multiplying by 12. No relationship was found

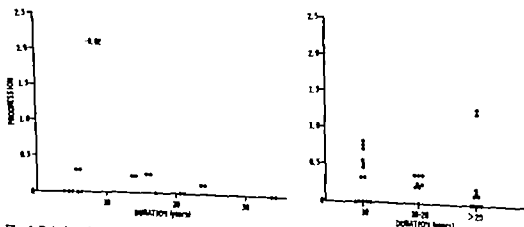


Fig. 1 Relation of progression of retinopathy to duration of diabetes. *A*, Progression of retinopathy in relation to duration of diabetes for each patient. *B*, Progression of retinopathy in relation to duration of diabetes in three periods—less than 10 years, 10 to 20 years, and more than 20 years.

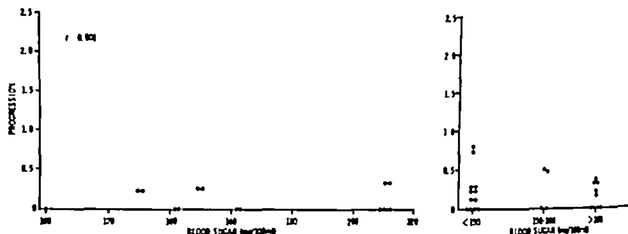


Fig 2 Relation of progression diabetic retinopathy to mean blood sugar level A Progression of retinopathy in relation to mean blood sugar for each patient. B Progression of retinopathy in a low (less than 150 mg per 100 ml) an intermediate (150 to 200 mg per 100 ml) and a high (more than 200 mg per 100 ml.) blood sugar group.

Table I Number of eyes showing progression in a low an intermediate and a high blood sugar group during a 36 month period with each feature of the retinopathy considered separately

Feature	No of eyes showing progression		
	Mean blood sugar <150 mg /100 ml (16 eyes)	Mean blood sugar 150 to 200 mg /100 ml (13 eyes)	Mean blood sugar >200 mg./100 ml. (16 eyes)
Background	0	2	3
Hemorrhages	2	1	3
New disc vessels	3	6	5
New retinal vessels	6	5	4
Fibrous tissue	4	2	4

between progression of retinopathy and age at observation (Bravais-Pearson correlation coefficient r = −0 01) progression of retinopathy and age at diagnosis (r = 0 04) or progression of retinopathy and duration of diabetes (Fig 1 r = −0 02) Similarly there was no relationship between progression of retinopathy and mean blood sugar level measured at clinical attendances (Fig 2 r = 0 001)

Each feature of the retinopathy was also considered separately over a period of 36 months (Table I) A trend toward more rapid progression of background retinopathy was apparent with higher blood sugar levels but this was not significant statistically No such trend was seen with other features and when new disc vessels, new retinal vessels, and fibrous tissue formation were considered together progression was identical in the low intermediate and high blood sugar groups. Progression of proliferative retinopathy was, therefore, unrelated to blood sugar level, which is in agreement with the conclusion of Kohner [14] who similarly used fundal photography

That the progression of retinopathy was unrelated to age or duration of diabetes agrees with the findings of Schlesinger and associates,[15] but Miki and associates[11] concluded that progression was more rapid in older patients.

The influence of age duration of diabetes, and blood sugar level on the natural history of established diabetic retinopathy remains open to doubt. The solution to the problem may be found in local ocular factors. It has been found that hypertension[16] and ocular hypotony[17] exert a deleterious effect on diabetic retinopathy whereas carotid artery stenosis,[18] central retinal artery occlusion,[19] glaucoma [20] and myopia[21] may have a protective effect. Duane and associates [9] have suggested that the net vascular pressure ratio is important, a high ratio between intravascular and intraocular pressure being associated with more severe retinopathy However the predominant factor in most patients remains obscure and further studies are needed to establish the relative importance of local and general factors which might influence the history of this condition.

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Propranolol in hypertension

The search goes on for the ideal hypotensive drug. Among the milder remedies the thiazide diuretics are widely accepted and are likely to retain their place in combination with the more potent drugs. In the days of pentolinium and mecamylamine, the physician required a sense of missionary zeal to make some patients continue their regimes in the face of intolerable side effects. It was logical that the next development should be the adrenergic neurone blocking drugs, such as guanethidine, bethanidine, and debrisoquin and the decarboxylase-inhibitor methyldopa. Even these remedies have serious drawbacks, such as postural, exercise, and hot weather hypotension and drowsiness. The advent of a drug, which has none of these features and which is capable of lowering blood pressure equally in standing, sitting, and lying positions, is worthy of careful study

Propranolol, we believe, is such a drug. Although this remedy has been studied for more than 6 years, the majority of physicians remain sceptical of its value and certainly would not regard it as a first line drug. The earlier controlled trials seemed to support this view However the very great variability in effective dosage was alluded to by Prichard six years ago[1] and has been apparent to us for more than 4 years. For example, we have found in a series of more than 300 patients studied for up to five and one-half years that no less than 40 per cent required a dose of 480 mg. per day or more, and 20 per cent required 1000 mg. per day or more for satisfactory control. By contrast, in none of

the controlled trials using arbitrary schedules did the dose of propranolol exceed 480 mg. per day and in most it was much less. Such trials could not be expected to yield conclusive results.

The discrepancy between the experiences of Pritchard and ourselves on the one hand and the controlled trials on the other hand led us to use an alternative approach. From our large series we selected 28 patients who, having been inadequately controlled on thiazides alone, had subsequently been well controlled with propranolol as well.[3]

Their dose of propranolol was known, their blood pressures had been stabilized for one to 4 years, the only variable factor in the trial was the presence or absence of propranolol. After a randomized double-blind crossover trial of 2 × 16 week periods it was clear that propranolol caused a statistically significant fall in blood pressure compared with the placebo. When propranolol was withdrawn the blood pressure rapidly rose to hypertensive levels but not to untreated levels, probably because of the diuretics. In our larger series we have accepted as a criterion of good blood pressure control a sitting diastolic pressure averaging less than 100 mm. Hg. By this standard more than 85 per cent of our patients are well controlled. Our results bear comparison with any of the established regimes.

How propranolol lowers blood pressure is not clearly known, but it certainly differs from the adrenergic neurone blocking drugs. We believe that it is a valuable hypotensive drug not only in its own right, but also in combination with other remedies in that very small group of highly resistent cases in which multiple regimes are needed and side effects are likely to be severe.

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Letters to the Editor

Storage of contrast material for angiocardiography

To the Editor:

Many years ago, we became disenchanted with the procedure of heating contrast agents in a water bath for injection into the cardiovascular system. The contrast material was usually overheated, or underheated, or not heated at all.

It is quite apparent that dye overheated could—and we would be inclined to believe *has*—caused problems to the patient as well as complications. Contrast agent heat should be at body temperature to decrease viscosity at the time of injection as well as provide for a more physiological procedure.

We came upon a simple solution for the problem of heating and storing of contrast agent and that is the use of a simple incubator set at body temperature (98.6° F.) or a degree or so above. Our incubator holds 24 vials of contrast agent and is stocked at the end of each day. The dye is uniformly heated and held at body temperature and is withdrawn as needed from the incubator and injected into the patient. We have a feeling of security because the agent is temperature controlled.

Numerous visitors to our laboratory have gone away with this idea and have put it to use in their own laboratories with gratifying results.

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The onset of atrial fibrillation in man

To the Editor:

Five years ago a paper "Mode of onset of atrial fibrillation in man," was published in the American Heart Journal. Time and uncritical acceptance appear to have raised the conclusion of the article to the dignity of textbook stature, for it is now quoted out of context as unqualified fact.[1,2] Unfortunately, the lack of precision inherent in the title and the characteristics of the patients studied have been disregarded.

One may take issue with the use of the generic term, "man," in the title. True all subjects studied qualified as man, but man of a particular kind. All had previously fibrillated, all had been electrically cardioverted, and all, following an atrial premature contraction (APC) within a defined coupling index, had reverted to atrial fibrillation. Man, in the generic sense, does not have these characteristics.

Table I. Observed results

CI (sec.)	*No arrhythmia*	*Atrial fibrillation*	*Atrial tachycardia*	*Total*
<0.48 ± 0.03	16	1	6	23
>0.48 ± 0.03	96	5	26	127
Total	112	6	32	150

The authors defined the coupling index (CI) as the ratio of P – P'/P – P in seconds, where P – P' was the interval between the premature P and the preceding normal sinus P wave and P – P was the time interval between the two preceding normal P waves. They concluded that atrial fibrillation may occur when the coupling ratio is 0.48 ± 0.03 or less. This appeared to be debatable if applied to a larger population of man in the general sense. To test the validity of the conclusion the courses of 150 patients with two or more APC's in 18 second rhythm strips were reviewed and the resulting arrhythmias, if any, identified. In this group, 67 had arteriosclerotic, 15 arteriosclerotic hypertensive, and 12 rheumatic heart disease. No cardiac disorder was present in 56 patients. None of these patients had previously fibrillated. The results are shown in Table I and from them the immediate impression is that, in a man who has not previously fibrillated, an APC within or beyond the CI has little effect in producing atrial fibrillation, or even atrial tachycardia. If the figures are subjected to the χ^2 test, χ^2 is 0.338 with two degrees of freedom. One must conclude that the effect of an APC, regardless of the CI in 85 per cent of cases, is due to chance or to other factors (such as atrial hypertrophy, distension, or ischemia) which apparently are more important in the production of atrial fibrillation. The CI, as defined, may be a critical factor in previous fibrillators but it should not be applied indiscriminately as a prognostic index in patients who have never fibrillated.

Hopefully, it will not take five more years for this misapplication of the coupling index to be deleted from textbooks.

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Reply

To the Editor:

Thank you for the opportunity to reply to the letter from Richard J. Kennedy, M.D., questioning the significance of the observations and conclusions described in the paper by Dr. Gault and me, "Mode of onset of atrial fibrillation in man," which appeared in the AMERICAN HEART JOURNAL.[1] In that paper we reported our findings in a group of patients observed closely following DC conversion. In each of 18 instances of relapse into atrial fibrillation, the arrhythmia was preceded by a closely coupled atrial premature beat. Control observations were made by measuring the coupling intervals in two populations of atrial premature complexes (APC's): (1) APC's in patients who did not relapse into fibrillation during the period of observation, and (2) those APC's in the patients who did relapse which were not followed by fibrillation. The coupling index (CI), calculated by comparing the ratio of the coupling interval to the length of the previous beat, was analyzed to provide a convenient index for the degree of prematurity of the APC in relation to the basic heart rate.

It was shown that the CI of those premature contractions which initiated atrial fibrillation was significantly shorter than the CI of atrial premature contractions which were not followed by fibrillation. In some instances fibrillation was preceded by an accelerating atrial tachycardia. We concluded that a spontaneously occurring atrial premature impulse may initiate atrial fibrillation. Furthermore, we suggested that the propensity of a premature impulse to initiate fibrillation is related to its relative prematurity and noted that when the CI is less than 0.50 in the patients studied the chance of fibrillation is high and conversely when the index is greater than 0.60 the chance of fibrillation is small.

Our observations have recently been confirmed by Bennett and Pentecost.[2] These authors show that atrial premature complexes preceding atrial fibrillation have a significantly shorter coupling time than those which do not initiate fibrillation (Fig. 7). They extend our observations by pointing out that the atrial premature beat was followed by accelerating atrial tachycardia which always preceded the onset of atrial fibrillation. It has been particularly gratifying to Dr. Gault and me to find that our earlier observations, based entirely on scalar electrocardiography, have been confirmed by workers whose data are based on direct atrial recordings.

Review of our 1965 paper stimulated by Dr. Kennedy's letter reaffirms our belief that the data are accurate and the conclusions reasonable. The actual value of the CI in a given patient is not important. The observation that atrial fibrillation is initiated by the more premature APC's seems valid. As discussed in the paper, this relationship has important implications regarding the concept of vulnerability and the genesis of arrhythmia in man.

The data presented by Dr. Kennedy are difficult to interpret. He states that the records of 150 patients with two or more APC's were reviewed. However, he presents data on only 150 premature beats rather than 300 or more which were available for analysis. One must ask how the decision to select a given APC for measurement was made. It is not clear why the cutoff value for CI is described as 0.48 ± 0.03 second. Since this is a ratio, the seconds cancel out, and the significance of the ±0.03 is unclear. Furthermore, Dr. Kennedy has compared the coupling indices of a heterogeneous group of patients in an attempt to refute the significance of a short coupling interval in the genesis of fibrillation. The data would be far more convincing if the CI's of a series of APC's in a given patient were compared.

A careful study of the onset of atrial fibrillation which failed to demonstrate a relationship between the degree of prematurity of an APC and the genesis of atrial fibrillation would be of considerable scientific interest. I have little doubt that such a study, subject of course to the usual peer review, would have easy access to the pages of a reputable scientific journal.

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Rebuttal

To the Editor:

The letter commenting on the "Mode of onset of atrial fibrillation in man" aimed at brevity. This answer to Dr. Killip's reply must sacrifice some of that quality.

In the 150 patients studied, the coupling indices (CI's) of all atrial premature complexes (APC's) were measured, but only the shortest index in each patient was considered, since the original paper stated that atrial fibrillation was more likely to occur after the shortest coupling interval. The cut

off time of 0.48 ± 0.03 emphasized in the article was used because the authors considered trial fibrillation more likely to occur at these intervals or less.

A heterogeneous group was deliberately selected to determine whether the CI applied t man in general. Such was not the case, as contrasted with the small selected group with the clinical charac teristics described in the original study of Drs. Killip and Gault. The point I raise and believe to be substantiated is that the CI is of no prognostic value in heterogeneous population without the characteristics of the patients in the original study or in the eight postinfarction patients of Bennett nd Pentecost who were all digitalized and had previously fibrillated or had frequent atrial ectopic ac tivity Unfortunately the concept of the CI has been carried over into medical texts without qualification. This, of course, is not the responsibility of the uthors.

The sentence in the reply that the actual value of the CI in given patient is not impor tant is surprising for as I interpret the paper the main burden of their conclusion was that an APC within the stated CI or less was most significant in the production of atrial fibrillation.

Dr Killip lists two populations. (1) APC' in patients who did not relapse into fibrillation nd (2) those APC' in patients who did relapse which were not followed by fibrillation. Into what did this second group relapse—into APC' ?

I agree that atrial fibrillation may be initiated by an APC or rapid trial tachycardia, but factors such as atrial tachycardia, distension, and hypoxemia influence the vulnerable period of the atrium so that rigid CI is not predictive of the onset of atrial fibrillation in heterogeneous population.

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A case of acute myocardial infarction with an atypical symptomatology: Cutaneous itching

To the Editor:

In relatively large percentage of cases of myocardial infarction the symptomatology may be atypical and in some cases so different from the classic pattern as to imitate other diseases or t make the diagnosis impossible.

One of my patients showed a peculiar pattern which I have never found mentioned in medical literature. This was mn aged 60 with no previous cardiac symptoms but only some digestive troubles, who upon going to bed one night had a sudden attack of severe itching as soon as he lay down in the bed. The itching was over the whole body including the legs, although more intense around the shoulders and arms. It was so violent that the patient was obliged to get out of bed and walk around for about 20 minutes trying to get relief Pallor and perspiration appeared, but no pain, nausea, or breathlessness. The itching was relieved with an analgesic suppository the patient went to sleep and the next day felt perfectly well. An electrocardiogram recorded 3 days later showed typical recent posterolateral infarction. H had a normal course and a complete recovery Now seven years later the patient is in excellent condition with only electrocardiographic signs of the old myocardial scar

I would be very interested to know if similar cases have been observed by others.

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Book reviews

THE PERICARDIUM AND ITS DISORDERS. Edited by Felix M Cortes M D Springfield Ill., 1971 Charles C Thomas, Publisher 298 pp. Price $15.50.

This relatively brief review of the pericardium and its disorders by Cortes and his contributing editors from Temple Medical School gathers together some of the present physiologic concepts and clinical states of interest to practicing physicians and students. The small monograph consists of 14 short chapters which summarize history anatomy congenital defects, diagnosis, graphic techniques, radiology hemodynamic phenomena, and various diseases with their medical and surgical management. The presentations are clear and concise with practical clinical aspect emphasized Although the book is not comprehensive it does present briefly and well pericardial diseases in a manner which should interest the busy physician. This monograph gathers in one publication the important aspects of diseases of the pericardium for busy clinicians. They will find it useful

ANTIKOAGULANTIEN UND FIBRINOLYSETHERAPIE. By Jurgen Jaenecke Stuttgart, 1971 Georg Thieme Verlag 158 pp.

This small book briefly reviews the problems related to anticoagulants and fibrinolysins. It includes history chemistry pharmacology antagonists, techniques, clinical indications, and anticoagulant and fibrinolysin therapy Heparin, Coumadin, and other anticoagulant agents are discussed The use of streptokinase and urokinase is also presented briefly This is a good short and useful publication which should interest students and physicians alike. The recent interest in streptokinase and urokinase makes that aspect of the book more timely

SYMPOSIUM ON CARDIAC ARRHYTHMIAS, ELSINORE, DENMARK APRIL 23–25 1970. Edited by Erik Sandoe Ellen Flensted Jensen, and Knud H Olesen, Sodertalje, Sweden 1971 published by AB Astra, 826 pp.

This is the proceedings of a symposium on cardiac arrhythmias held in Elsinore Denmark from April 23 to 25 1970. Like all such publications, this book enables every reader to profit by studying the presentations at leisure even though he was not in attendance at the symposium. Again, as is true of all symposia these days, numerous papers review many of the problems and are followed by discussions by the participants. This is a good volume which includes discussions of pathophysiology electrophysiology diagnosis, recording and management of an extremely important aspect of cardiology This book is worth owning

SIMPLIFIED VECTORCARDIOGRAPHY By Jozef Wartak, M D B.Sc. Philadelphia Toronto, 1970, J B. Lippincott Company 182 pp. Price $ 1.50.

Wartak has presented a simplified review of vectorcardiography There is, of course, nothing new in this book, except that the author describes his approach to vectorcardiography The concept of the electric activity of the heart is briefly reviewed with the aid of simple diagrams. The application of vector analysis is discussed along with techniques, equipment used in the recording of tracings, methods of analysis, and normal patterns and tracings in various common disease states. The bibliography is good although not complete. The clear short text, with its simple illustrations placed to the side of the text on the same page is welcomed This is a good book for beginners, provided they do not limit their study ing to this one source The author fails to emphasize that vectorcardiography is really a supplement to electrocardiography and should be interpreted in association with the latter Vectorcardiography in its present state cannot replace electrocardiography in clinical practice.

SYMPOSIUM SUR L INSUFFISANCE CARDIAQUE DEBUTANTE (SYMPOSIUM ON INCIPIENT CARDIAC INSUFFICIENCY). Symposium de la Société Européene de Cardiologie (Symposium of the European Society of Cardiology) Locarno, April 8-11 1970 Basel, 1970, Sandoz Ltd 400 pp.

These proceedings of a symposium on incipient cardiac insufficiency which was held during April 1970 consist of papers summarizing presentations related to morphologic, biochemical, physiologic, pathologic, clinical and diagnostic and treatment of myocardial insufficiency As with symposia these days nothing new is contained in the publication. Various people gather and discuss their work. Some are actively engaged in related studies and others are not. There is a great deal of discussion which is good if there is vigorous follow up of ideas when the participants return to their respective laboratories, hospitals, and offices. In general, symposia of this sort are good and published proceedings help readers interested in the field who can critically evaluate the presentations. This publication of the sym-

posium on myocardial insufficiency contains considerable amount of panel discussions which are interesting. The original papers are short, too short to provide the reader with an adequate orientation of the entire field discussed by any of the authors. Therefore, the reader of the proceedings must study the literature carefully and extensively to learn the problems involved in myocardial insufficiency and impending and early congestive heart failure. These proceedings are interesting and apparently summarize the most important thoughts and concepts in the mind of the respective authors and discussants concerning their selected problems of myocardial insufficiency. It is always interesting to this reviewer to observe what other people think about important cardiac problems. A critical examination of these presentations affords others who were not present at the symposium an opportunity to learn the thoughts of the participants.

Books received

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Editorial

Localization and significance of atrioventricular block

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Within recent years an abundance of information has become available concerning the pathology electrophysiology anatomy and clinical significance of disturbances of atrioventricular (A V) conduction. Interest on this subject apparently began in 1827 with a description by Adams[1] of syncope associated with a slow heart rate and subsequent observations by Stokes[2] In 1846 Wenckebach[3] (1899) and Hay[4] (1906) described atrioventricular conduction block and ushered in the era of eponyms and synonyms in the classification of atrioventricular conduction disturbances. The issue heated up intensely in 1924 when Mobitz[5] classified A V block according to rather precise criteria. In the following years, numerous clinical and experimental studies appeared in the medical literature. Katz, in 1941 attempted to describe the clinical correlation in the presence of various types of A V block. Uhley and Rivkin[7,8] first described the ECG pattern following the interruption of the main and peripheral branches of the canine right (1961) and left (1964) bundle branch system and in 1963 Lenègre[9-11] and Lev[12] initiated the intense anatomical studies that led to the more recent concepts of intraventricular conduction disturbances. Precise experimental studies by Lenègre,[9-11] Lev[12] Pruitt,[13] and Rosenbaum[14] offered a logical classification of block within the fascicles of the Purkinje system By the mid 1960's, Hoffman and Cranefield[15] Paes de Carvalho[16] Watanabe and Dreifus[17,18] and others had explored the electrophysiologic mechanisms of atrioventricular conduction delay at the cellular level. Studies in man using His-bundle electrograms by Damato and associates[19] and Narula and coworkers[20-22] confirmed the findings in earlier animal experiments. However the importance of a more precise classification of A V block came into sharp focus with the development of electronic pacing and the dramatic lifesaving results which followed. Unfortunately too little is known about the life expectancy in patients with A-V block, and the medical literature is often distorted by a few scattered cases with unusually long survival or by including cases of A V block engendered by an acute myocardial process.[23] It is our intention to review the present anatomic, electrophysiologic, and clinical knowledge in an attempt to define A V conduction disturbances. It is probably wise to consider first the classical definitions set forth by Wenckebach[3] and Mobitz.[5,24]

Wenckebach in his original paper in 1899 described a progressive prolongation of the a-c interval (interval between atrial and ventricular contractions) until one ventricular contraction dropped out. Following a pause the a-c interval was

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shortest, which suggests improved conductivity. Impairment of conductivity as judged from the increment of the a-c interval was most marked in the second conducted beat and much less in subsequent beats. This resulted in a quickening of the radial pulse. However, the increment of a-c interval was often again greater immediately before the dropped beat in the presence of higher conduction ratios, resulting in a slowing of the pulse. When Mobitz[4] for the first time classified incomplete A-V conduction disturbances in 1924, he termed the above variety Type I, which subsequently became known by the name of Wenckebach periodicity.

In contrast, Mobitz[24] called a block Type II when a ventricular complex dropped out without any change in the P-R interval of the electrocardiogram in immediately preceding beats. He also mentioned that in the Type II variety, often many successive ventricular beats dropped out causing prolonged asystole despite preceding periods of 1:1 conduction with a normal P-R interval. Hence, it must be re-emphasized that the original classification of the two types of "partial heart block" was based entirely on variation or constancy of the A-V conduction time.

The electrophysiologic mechanism of decremental conduction in the A-V junctional tissues (N region) was suggested by Hoffman and Cranefield,[13] Paes de Carvalho,[14] and Watanabe and Dreifus.[17,18] Marked interweaving and anastomosis of fibers as well as extremely slow and inhomogeneous conduction in the N region were suggested as possible explanations for this variety of slow decrement and block in this area.[17] However, additional delay was also noted below the A-V node and two areas of block could occur simultaneously.[17,23]

In contrast, electrophysiologic studies identified major block in the infranodal region and wide QRS complexes associated with the Type II variety, although concealed premature systoles or concealed re-entry could also engender the sudden dropping of the QRS complex.[17] Scherf and Shookhoff[26] produced both types by depressing conduction through the bundle branches. Kaufman and associates[27] noted a high incidence of pre-existing bundle branch block and offered the explanation of the development of bilateral bundle branch block for the Mobitz Type II variety. Lenègre[9,11] and Rosenbaum[14] described precise anatomic, electrocardiographic, and clinical studies of subjunctional block and brought into sharp focus the requirement for a detailed analysis of the electrocardiogram in these cases.

His bundle electrograms have added valuable evidence in determining the major areas of conduction block in both types of A-V block.[16] Narula and co-workers[27] confirmed that progressive prolongation of the P-R interval could be due to delay either above the His or in the subjunctional regions of the A-V transmission system. Hence, it is rather improbable that distinction between Types I and II can be made on the basis of the P-R interval.

Confusion occurs when one talks exclusively of the progressive or sudden increase of the P-R interval before the dropped beat in attempting to classify the two types of block, as this criteria can be applied only in the presence of regular supraventricular rhythm and second-degree A-V block associated with conduction ratios greater than 2:1.[23] Furthermore, instances of atrial fibrillation and higher grades of A-V block cannot be considered in this classification.

From the clinical standpoint, it is the location of the block that largely determines the significance, rather than the variation or constancy of the P-R interval. Mobitz originally described the high incidence of Adams-Stokes attacks as well as complete heart block in cases of Type II variety. Later, Katz[6] and Donoso and associates[29] confirmed the sinister prognosis associated with block and wide QRS complexes. Similar observations were made by Lenègre,[11] Scanlon,[30,31] and Halat[32] and their co-workers. In the latter study, major neurologic or cardiac symptoms were present in 86.2 per cent of patients with A-V block associated with wide QRS complexes as contrasted to 37.5 per cent of those patients with narrow QRS complexes. Furthermore, the incidence of sudden cardiovascular death was more than twofold in the group with wide QRS complexes.

Second-degree and high-grade A V block offered a similar prognosis.[23]

With the development of cardiac pace makers as well as the expanding knowledge in precise localization of the pharmacologic action of antiarrhythmic and cardiotonic agents the clinician must acquire a firm understanding of the nature of A V transmission. Digitalis acetylcholine and ischemia appear to slow intranodal conduc tion while procaine amide, qu nidine propranolol potassium salts and lidocaine slow conduction above the A V node and in the subjunctional region.[20-22] For prac tical purposes, the site of block can be identified by the duration of QRS n most instances, and His-bundle electrocardiog raphy will add little to clinical manage ment. If progressive P R prolongation is seen w th a wide QRS complex, two levels of block may be present, but therapy is predicated on the lowest level of block. Conduction delay of the Wenckebach variety is most common in the N region of the A V node but can be seen in the subjunctional region of the A V transmission system[25] and even between con tiguous ventricular fibers,[26] but offers little as a prognostic sign alone

Determination of the varieties of A V block is predicated on the precise identifica tion of the site(s) of conduction delay as prognosis and therapy must follow on this basis. Further electrophysiologic and phar macologic stud es will undoubtedly reveal other mechanisms on the nature of A V transmission.

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Clinical communications

Hemodynamic studies with sotalol in man performed at rest, during exercise, and during right ventricular pacing

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It has been demonstrated in experimental animals and in man that sotalol 4-(2-isopropylamino-1 hydroxyethyl) methanesulfonanilide (MJ 1999) is a selective beta-adrenergic blocking agent with low toxicity.[1-4] Some investigators have reported that, in contradistinction to propranolol, it is without significant direct depressant effect on the force of myocardial contraction.[1-4] On the other hand, Blinks found depression of cardiac contractility in electrically driven papillary muscles and left atria of guinea pigs and kittens treated with sotalol at concentrations as low as 10 M, which is only slightly greater than the dose at which initial beta-blocking effect was noted.

This study was carried out in order to investigate the hemodynamic changes induced by sotalol in man at rest, during exercise, and during controlled (paced) ventricular rate.

Material and methods

The study was performed on 24 male patients between 34 and 58 years of age (mean 48) who were undergoing diagnostic cardiac catheterization. Ten patients had coronary artery disease, 7 had rheumatic heart disease, 3 were found to have a normal heart, and the other 4 had, respectively, idiopathic hypertrophic subaortic stenosis, left bundle branch block with normal coronary arteries, aortic insufficiency of unknown etiology, and idiopathic nonobstructive cardiomyopathy. The patients were premedicated with a combination of morphine (7.5 to 15 mg.) and scopolamine (0.02 to 0.04 mg.) or meperidine (50 to 100 mg.) and secobarbital (100 mg.) intramuscularly.

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Clinical communications

Hemodynamic studies with sotalol in man, performed at rest, during exercise, and during right ventricular pacing

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It has been demonstrated in experimental animals and in man that sotalol 4-(2-isopropylamino-1 hydroxyethyl) methanesulfonanilide (MJ 1999) is a selective beta-adrenergic blocking agent with low toxicity.-4 Some investigators have reported that, in contradistinction to propranolol, it is without significant direct depressant effect on the force of myocardial contraction.[2-4] On the other hand, Blinks found depression of cardiac contractility in electrically driven papillary muscles and left atria of guinea pigs and kittens treated with sotalol at concentrations as low as 10^{-4}M which is only slightly greater than the dose at which initial beta-blocking effect was noted.

This study was carried out in order to investigate the hemodynamic changes induced by sotalol in man at rest, during exercise, and during controlled (paced) ventricular rate.

Material and methods

The study was performed on 24 male patients between 34 and 58 years of age (mean 48) who were undergoing diagnostic cardiac catheterization. Ten patients had coronary artery disease, 7 had rheumatic heart disease, 3 were found to have a normal heart, and the other 4 had, respectively, idiopathic hypertrophic subaortic stenosis, left bundle branch block with normal coronary arteries, aortic insufficiency of unknown etiology, and idiopathic nonobstructive cardiomyopathy. The patients were premedicated with a combination of morphine (7.5 to 15 mg.) and scopolamine (0.02 to 0.04 mg.) or meperidine (50 to 100 mg.) and secobarbital (100 mg.) intramuscularly

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Table I Hemodynamic studies with sotalol at rest

Variable	N	Mean		Mean difference	% change	Significance of difference
		Control	p Sotalol			
Ventricular rate (beats/min.)	14	89	76	13	−15	$p < 0 01$
Arteriovenous oxygen difference (volumes/100 ml.)	14	5 5	6 4	0 9	16	$p < 0 001$
Cardiac index (L./min./M^2)	14	2 4	2 0	0 4	−17	$p < 0 001$
Stroke volume index (ml./beat/M^2)	14	27	27	0	0	N.S.
Left ventricular end-diastolic pressure (mm. Hg)	14	10	1	2	20	$p < 0 01$
Mean pulmonary artery pressure (mm. Hg)	14	23	24	1	4	N.S.
Total pulmonary resistance index (dynes-sec.-cm.$^{-5}$ M^2)	14	820	990	170	21	N.S.
LV dP/dt (mm Hg/sec.)	13	1 610	1 360	250	−16	$p < 0 01$
Mean systemic arterial pressure (mm. Hg)	7	89	92	3	3	N.S.
Total systemic resistance index (dynes-sec -cm.$^{-5}$-M^2)	7	3 010	3 450	440	15	$p < 0 05$
Left ventricular work (Kg M /min./M^2)	7	0 31	0 27	0 04	−14	N.S.

N = Number of subjects.
N.S. = Not statistically significant ($p > 0.05$)

In each patient right and left heart catheterizations were performed from a cutdown on the brachial artery and vein using a No 7F Cournand catheter and a No 7F or No 8F Eppendorf catheter

In 10 patients a No 5F bipolar pacing catheter was positioned at the apex of the right ventricle and the heart was paced at a constant rate throughout the study

In all patients a left ventricular cineangiogram was obtained by using 45 c c of 85 per cent meglumine diatrizoate (Cardiografin) injected at 15 c c per second Selective coronary angiography was performed in 17 patients with the use of 76 per cent meglumine diatrizoate (Renografin)

Cardiac output was calculated by the Fick method Oxygen consumption was predicted at rest according to the surface area sex and age and was measured during exercise before and after sotalol in 7 patients. In the eighth patient (studied during exercise) the oxygen consumption during exercise was assumed to be the same after sotalol as before, with the exercise conditions being the same (That exercise levels were the same before and after sotalol is indicated by similar oxygen consumptions whenever these were measured [Table III]) Expiratory volume was measured with a Parkinson Cowan spirometer and the air samples were analyzed for O_2 and CO_2 by the Scholander technique[18] The blood gas and hemoglobin determinations were performed with a pH gas analyzer (Model 113) and a CO-oximeter (Model 182) both from Instrumentation Laboratory Inc.

Pressures were measured with Statham P23Db pressure transducers, with zero reference midway between sternum and spine and were recorded on an oscillographic recorder (DR-8 Electronics for Medicine)

Sotalol was given over a period of 5 minutes into the main pulmonary artery with the dose ranging from 0 1 mg per kilogram in the first study to 0 5 mg per kilogram in the later ones. Pressures were recorded from the pulmonary artery and the left ventricle immediately before immediately after and

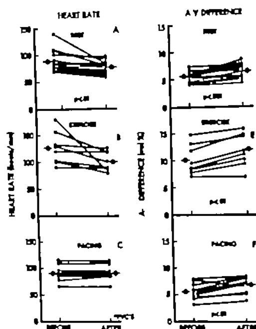


Fig. 1 The heart rate and arteriovenous oxygen difference (*A V difference*) before and after administration of sotalol are shown for 14 patients at rest, for 8 patients during exercise, and for 10 patients during constant-rate right ventricular pacing (*R.V. pacing*). The statistical significance of the difference between paired variables is indicated at the bottom of each figure. N.S., Not significant.

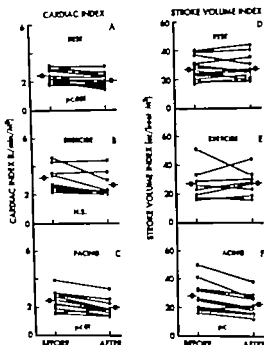


Fig. 2. The cardiac index and stroke volume index before and after administration of sotalol are shown for 14 patients at rest, for 8 patients during exercise, and for 10 patients during right ventricular pacing.

5, 10, and 20 minutes after sotalol in 23 patients. Systemic blood pressure was measured directly in the central aorta in 9 patients, and indirectly in 3 patients with a sphygmomanometer on the arm before and 20 minutes after sotalol. Pulmonary artery "wedge" pressure was measured in 8 patients before and 20 minutes after sotalol. When exercise was performed, 10 minutes or more of subsequent rest was allowed before sotalol was given.

Left ventricular dP/dt was electronically computed from externally measured left ventricular pressure with an RC differentiating circuit (Model RC 1, Electronics for Medicine).

Standard statistical analyses were performed with the aid of a small desk top computer (Olivetti Underwood Programma 101). The significance of the difference between the means of paired variables was determined using the Student t test (with $p < 0.05$ being accepted as a significant difference).

Results

The studies on 24 patients were performed under three different conditions: (1) rest—14 patients, (2) exercise—8 patients, (3) constant rate right ventricular pacing—10 patients. Some patients were studied under more than one condition. Not every parameter was measured in each patient.

I. Hemodynamic studies at rest. The mean values of each parameter (before and after sotalol), number of patients studied (N), per cent change induced by sotalol, and the significance of the change after sotalol are shown in Table I. The dose of sotalol administered intravenously ranged from 0.1 to 0.5 mg. per kilogram with an average of 0.34 mg. per kilogram. There was a statistically significant decrease in heart rate (Fig. 1,*A*), cardiac index (Fig. 2,*A*), and left ventricular dP/dt (Fig. 3,*D*). Arteriovenous oxygen difference (Fig. 1,*D*), left ventricular end-diastolic pressure (LVEDP) (Fig. 3,*A*), and total systemic resistance (Fig. 5,*D*) all increased significantly. The 17 per cent decrease in cardiac index at rest

Table I. Hemodynamic studies with sotalol at rest

Variable	N	Mean: Control	Mean: p Sotalol	Mean difference	% change	Significance of difference
Ventricular rate (beats/min.)	14	89	76	13	−15	$p < 0.01$
Arteriovenous oxygen difference (volumes/100 ml.)	14	5.5	6.4	0.9	16	$p < 0.001$
Cardiac index (L./min./M.^{2})	14	2.4	2.0	0.4	−17	$p < 0.001$
Stroke volume index (ml./beat/M.^{2})	14	27	27	0	0	N.S.
Left ventricular end-diastolic pressure (mm. Hg)	14	10	12	2	20	$p < 0.01$
Mean pulmonary artery pressure (mm. Hg)	14	23	24	1	4	N.S.
Total pulmonary resistance index (dynes-sec.-cm.$^{-5}$-M.^{2})	14	820	990	170	21	N.S.
LV dP/dt (mm. Hg/sec.)	13	1,610	1,360	250	−16	$p < 0.01$
Mean systemic arterial pressure (mm. Hg)	7	89	92	3	3	N.S.
Total systemic resistance index (dynes-sec.-cm.$^{-5}$-M.^{2})	7	3,010	3,450	440	15	$p < 0.05$
Left ventricular work (Kg.-M./min./M.^{2})	7	0.31	0.27	0.04	−14	N.S.

N = Number of subjects.
N.S. = Not statistically significant ($p > 0.05$).

In each patient, right and left heart catheterizations were performed from a cutdown on the brachial artery and vein using a No. 7F Cournand catheter and a No. 7F or No. 8F Eppendorf catheter.

In 10 patients a No. 5F bipolar pacing catheter was positioned at the apex of the right ventricle and the heart was paced at a constant rate throughout the study.

In all patients a left ventricular cineangiogram was obtained by using 45 c.c. of 85 per cent meglumine diatrizoate (Cardiografin) injected at 15 c.c. per second. Selective coronary angiography was performed in 17 patients with the use of 76 per cent meglumine diatrizoate (Renografin).

Cardiac output was calculated by the Fick method. Oxygen consumption was predicted at rest according to the surface area, sex, and age and was measured during exercise before and after sotalol in 7 patients. In the eighth patient (studied during exercise) the oxygen consumption during exercise was assumed to be the same after sotalol as before, with the exercise conditions being the same. (That exercise levels were the same before and after sotalol is indicated by similar oxygen consumptions whenever these were measured [Table III].) Expiratory volume was measured with a Parkinson-Cowan spirometer and the air samples were analyzed for O_2 and CO_2 by the Scholander technique.[16] The blood gas and hemoglobin determinations were performed with a pH/gas analyzer (Model 113) and a CO-oximeter (Model 182), both from Instrumentation Laboratory, Inc.

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Sotalol was given over a period of 5 minutes into the main pulmonary artery, with the dose ranging from 0.1 mg. per kilogram in the first study to 0.5 mg. per kilogram in the later ones. Pressures were recorded from the pulmonary artery and the left ventricle immediately before, immediately after, and

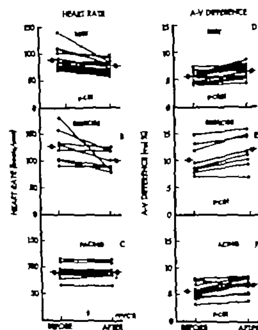


Fig. 1 The heart rate and arteriovenous oxygen difference (*A V difference*) before and after administration of sotalol are shown for 14 patients at rest, for 8 patients during exercise, and for 10 patients during constant-rate right ventricular pacing (*R.V pacing*) The statistical significance of the difference between paired variables is indicated at the bottom of each figure. *N.S.* Not significant.

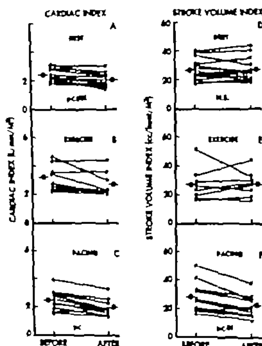


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5 10 and 20 minutes after sotalol in 23 patients. Systemic blood pressure was measured directly in the central aorta in 9 patients, and indirectly in 3 patients with a sphygmomanometer on the arm before and 20 minutes after sotalol Pulmonary artery "wedge" pressure was measured in 8 patients before and 20 minutes after sotalol. When exercise was performed 10 minutes or more of subsequent rest was allowed before sotalol was given

Left ventricular dP/dt was electronically computed from externally measured left ventricular pressure with an RC differentiating circuit (Model RC 1 Electronics for Medicine)

Standard statistical analyses were performed with the aid of a small desk top computer (Olivetti Underwood Programma 101) The significance of the difference between the means of paired variables was determined using the Student t test (with $p < 0.05$ being accepted as a significant difference)

Results

The studies on 24 patients were performed under three different conditions (1) rest—14 patients, (2) exercise—8 patients, (3) constant-rate right ventricular pacing—10 patients. Some patients were studied under more than one condition Not every parameter was measured in each patient.

I Hemodynamic studies at rest. The mean values of each parameter (before and after sotalol) number of patients studied (N) per cent change induced by sotalol and the significance of the change after sotalol are shown in Table I The dose of sotalol administered intravenously ranged from 0.1 to 0.5 mg per kilogram with an average of 0.34 mg per kilogram There was a statistically significant decrease in heart rate (Fig 1,*A*) cardiac index (Fig 2,*A*) and left ventricular dP/dt (Fig 3,*D*) Arteriovenous oxygen difference (Fig 1,*D*) left ventricular end-diastolic pressure (LVEDP) (Fig 3,*A*) and total systemic resistance (Fig 5,*D*) all increased significantly The 17 per cent decrease in cardiac index at rest is almost entirely accounted for by a 15

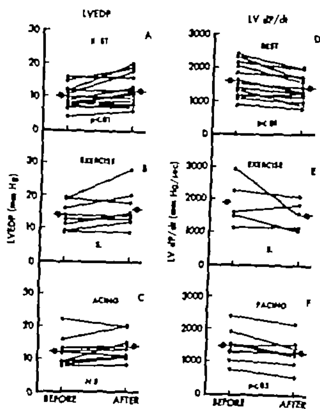


Fig 3 Left ventricular end-diastolic pressure (LVEDP) and left ventricular dP/dt (LV dP/dt) before and after administration of sotalol are shown for 14 and 13 patients respectively at rest 8 and 5 patients, respectively during exercise and 9 patients during RV pacing

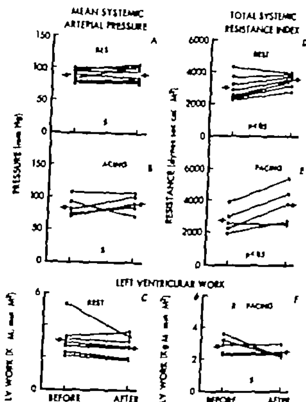


Fig 5 Mean systemic arterial pressure and total systemic resistance index before and after administration of sotalol are shown for 7 patients at rest and 5 patients during right ventricular pacing (A,B D,E) Left ventricular work before and after administration of sotalol is shown for 7 patients at rest and 5 patients during right ventricular pacing (C F)

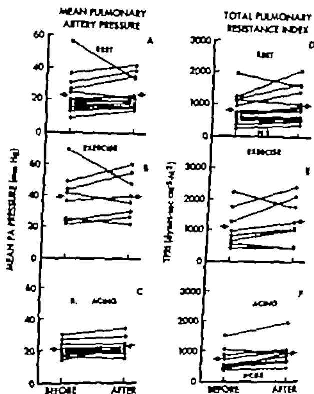


Fig 4 Mean pulmonary artery (PA) pressure and total pulmonary resistance index (TPRI) before and after administration of sotalol are shown for 14

per cent decrease in heart rate there was no significant change in stroke volume (Fig 2,D) No significant change was seen in mean pulmonary artery pressure (Fig 4,A) total pulmonary resistance (Fig 4,D) or mean systemic arterial pressure (Fig 5,A) Left ventricular work decreased in 6 of 7 patients studied but the changes were generally small and the average change was not statistically significant (Fig 5 C)

II Hemodynamic studies during exercise The mean values of each parameter before and after sotalol the per cent change, and statistical significance of the difference are given in Table II The dose of sotalol administered intravenously varied from 0 1 to 0 5 mg per kilogram with an average of 0 34 mg per kilogram. Each parameter was measured in 8 patients except for the left ventricular dP/dt which was measured in 5 patients, and the oxygen consumption in 7 patients.

As at rest there is approximately the same degree of decrease in

Table II Hemodynamic studies with sotalol during exercise

Variable	N	Mean		Mean difference	% change	Significance of difference
		Control	$\bar{p}$ Sotalol			
Ventricular rate (beats/min.)	8	127	101	26	−20	N.S.
Arterio-venous oxygen difference (volumes/100 ml.)	8	10 2	11 9	1 7	17	p < 0 01
Cardiac index (L./min./M.²)	8	3 2	2 7	0 5	−16	N.S.
Stroke volume index (ml./beat/M.²)	8	27	27	0	0	N.S.
Left ventricular end-diastolic pressure (mm. Hg)	8	14	16	2	14	N.S.
Mean pulmonary artery pressure (mm. Hg)	8	39	40	1	3	N.S.
Total pulmonary resistance index (dynes-sec.-cm.⁻⁵-M.²)	8	1 110	1 330	220	20	N.S.
LV dP/dt (mm. Hg/sec.)	5	1 890	1 520	370	−20	N.S.
Oxygen consumption (ml./min.)	7	585	570	5	1	N.S.

N Number of subjects.
N.S. = Not statistically significant ($p > 0.05$).

ventricular dP/dt (Fig 3,E) but the smaller number of patients studied and the variability of the data do not allow statistical significance. Again there was no change in average stroke volume (Fig 2,E) The increase in arteriovenous oxygen difference was significant at the 1 per cent level (Fig 1,E) Left ventricular end diastolic pressure (Fig 3,B) and total pulmonary resistance index (Fig 4 E) increased 14 and 20 per cent, respectively virtually the same degree as at rest but on exercise the changes were not significant. There was no change in mean pulmonary artery pressure (Fig 4,B)

III Hemodynamic studies at a constant ventricular paced rate. Because of the possibility that changes in cardiac index, arteriovenous oxygen difference, and left ventricular dP/dt could be secondary to slowing of heart rate without any basic change in myocardial contractility the study was performed in 10 patients whose heart rates were maintained constant by right ventricular pacing In one patient the heart rate increased slightly after sotalol because of interpolated premature ventricular beats (Fig 1 C) The mean values, average change induced by sotalol, and significance of the change are given in Table III. The dose of sotalol administered intravenously varied from 0.3 to 0.5 mg per kilogram with an average of 0 41 mg per kilogram. In spite of the fixed heart rate, the cardiac index (Fig 2 C) and stroke volume index (Fig 2 F) decreased 20 and 21 per cent, respectively ($p < 0.01$) Average left ventricular dP/dt (Fig 3 F) also decreased from 1 480 to 1,290 mm Hg per second ($p < 0.05$) Significant increases in arteriovenous oxygen difference (Fig 1 F) total pulmonary resistance index (Fig 4,F) and total systemic resistance index (Fig 5,E) occurred as well No statistically significant change occurred in LVEDP (Fig 3 C) mean pulmonary artery pressure (Fig 4,C) mean systemic arterial pressure (Fig 5,B) or mean pulmonary artery "wedge" pressure. Left ventricular work was measured in only 5 patients and did not change in 3 and decreased in 2 (Fig 5 F) The average change in left ventricular work was not statistically significant.

Discussion

The beta adrenergic blocking agents have proved to be useful in many clinical situations, including the treatment of arrhythmias, angina pectoris, obstruction of the left ventricular outflow tract secondary to idiopathic hypertrophic subaortic stenosis, and obstruction of the right ventricular outflow tract in tetralogy of Fallot.[11 13] However propranolol the

Table III Hemodynamic studies with sotalol at a constant ventricular paced rate

Variable	N	Mean		Mean difference	% change	Significance of difference
		Control	$\bar{p}$ Sotalol			
Arteriovenous oxygen difference (volumes/100 mL)	10	5 7	6 8	1 1	19	$p < 0.01$
Cardiac index (L./min./M.²)	10	2 5	2 0	0 5	−20	$p < 0.01$
Stroke volume index (ml./beat/M.²)	10	28	22	6	−21	$p < 0.01$
Left ventricular end-diastolic pressure (mm. Hg)	9	12	14	2	17	N.S.
Mean pulmonary artery pressure (mm. Hg)	9	21	23	2	10	N.S.
Total pulmonary resistance index (dynes-sec.-cm.⁻⁵ M.²)	9	730	950	220	30	$p < 0.05$
LV dP/dt (mm. Hg/sec.)	9	1 480	1 290	190	−13	$p < 0.05$
Mean systemic arterial pressure (mm. Hg)	5	81	91	7	8	N.S.
Total systemic resistance index (dynes-sec.-cm.⁻⁵ M.²)	5	2 720	3 730	1 010	37	$p < 0.05$
Left ventricular work (Kg. M./min./M.²)	5	0 29	0 25	0 04	−14	N.S.
Mean pulmonary artery "wedge" pressure (mm. Hg)	5	12	11	1	−8	N.S.

N = Number of subjects.
N.S. = Not statistically significant ($p > 0.05$)

used beta-adrenergic blocking agent produces significant depression of myocardial contractility both in animals[3, 8, 9] and in man.[16, 19] Newer beta-adrenergic blocking agents such as sotalol have been developed in hopes of decreasing the myocardial depressant properties while maintaining beta blockade.

The hemodynamic findings at rest in this study are compatible with those in some of the previous studies in animals[3, 8] and man[7] showing little or no intrinsic myocardial depressant effect other than that associated with slowing of heart rate. With a constant stroke volume before and after sotalol, the decrease in cardiac output (and increase in arteriovenous oxygen difference) can be attributed entirely to slowing of the heart rate. The decrease in dP/dt and slight increase in left ventricular end-diastolic pressure may also be a function of the negative chronotropic effect. V_m and other basic measures of myocardial contractility have been shown to vary directly with heart rate or stimulation rate.[20]

Two questions might be raised in regard to the validity of the left ventricular dP/dt data. First, said data were computed from left ventricular pressure measured with a catheter–external manometer system well known to have poor frequency response. Second, left ventricular dP/dt is a function of end-diastolic pressure (pre-load), peak aortic pressure (after load), and heart rate in addition to myocardial contractility.[21]

Left ventricular dP/dt computed from left ventricular pressure measured simultaneously through a catheter–external manometer system and a catheter tip manometer (Statham P-866) in dogs under various positive and negative inotropic conditions demonstrated that the dP/dt (and calculated V_{max}) from the catheter–external manometer system is a much less sensitive measure of inotropic change than the simultaneously measured dP/dt (and calculated V_{max}) from the catheter tip manometer.[22] Although the magnitude of change in V_{max} and dP/dt calculated from the catheter–external manometer system was much damped when compared with that from the catheter tip manometer, the direction of change was faithfully reflected. Thus, the decrease in dP/dt that occurred ... lol

may be an underestimate but probably reflects a true change lack of significant change in dP/dt as observed by a catheter-external manometer system does not necessarily mean that changes have not occurred

Finally the question of the variability of dP/dt with factors not directly related to myocardial contractility can be answered by noting that there was no change in mean systemic arterial pressure (after-load) and that the change in LVEDP (pre-load) although small was in such a direction as to increase dP/dt. Thus, the only variables left to account for the decrease in dP/dt are the negative chronotropic effect and a decrease in myocardial contractility and the studies during pacing are of particular interest in that the negative chronotropic effect is eliminated as well as the effect of heart rate on inotropism[19,22,24]

It would have been predicted from the studies at rest and during exercise that relatively little change in cardiac function would be seen when heart rate was maintained constant however such was not the case. It must be concluded that the decrease in cardiac index and stroke volume index and increase in arteriovenous oxygen difference during right ventricular pacing represent an actual negative inotropic effect. The decrease in left ventricular dP/dt is also a valid measure of myocardial depression since heart rate and arterial pressure (after-load) were constant and the change in left ventricular end-diastolic pressure (pre-load) although not significant, was in such a direction as to increase dP/dt.

The hemodynamic changes during exercise after the administration of sotalol are generally in the same direction and of the same order of magnitude as at rest, but because of the greater variability of the data and fewer patients studied they are not of statistical significance, with the exception of the increase in arteriovenous oxygen difference. Although not significant, the decrease in cardiac index is almost entirely accounted for by the decrease in heart rate while the stroke volume remains constant.

We conclude that sotalol does have a negative inotropic effect on the human myocardium. However this need not be separate from its beta-adrenergic blocking properties. Hoffmann and Grupp[4] have demonstrated that in the dog most of the negative inotropic effect of sotalol disappears in the reserpinized preparation suggesting that its myocardial depressant action is due to beta-adrenergic blockade. This is in contrast to propranolol in that most of the negative inotropic effect of propranolol remains in the reserpinized preparation indicating a direct depressant effect separate from beta-blockade.

The response to sotalol of heart rate cardiac index, stroke index arteriovenous oxygen difference, pulmonary artery pressure, and systemic arterial pressure at rest in this study with an average dose of 0.34 mg per kilogram was virtually identical to that reported by Brooks and associates[22] with a dose of 0 4 mg per kilogram. They report a 20 per cent decrease in heart rate and a 19 per cent decrease in cardiac index but no change in stroke volume index. Arteriovenous oxygen difference increased significantly in their study but there was no change in mean pulmonary artery pressure or mean systemic arterial pressure. In contrast to our study in which a small but significant increase in LVEDP was demonstrated (LVEDP rose in 9 patients, was unchanged in 5 and dropped in none) their study demonstrated no change in LVEDP They did not repeat their studies during exercise or fixed-rate pacing

The comparison of the hemodynamic effects of sotalol with those of propranolol will be important in determining the ultimate clinical usefulness of sotalol. A direct comparison was not made in this study nor has it been reported in other human studies. Direct comparisons have been carried out in animals,[4,9,22] and indirect comparison in man can be made by relating this study to previous similar hemodynamic studies using propranolol[14-16]

In a comparison of the two drugs, a standard for deriving comparable potency must be determined For the beta adrenergic blocking agents this has usually been the effect of the agent in blocking one of the beta-receptor effects of isoproterenol. Propranolol is about ten times more potent than sotalol when tested in rabbit atria, three times more potent in the cat,[4] and four to ten times more potent in the dog[4,24] Relative beta-blocking potency studies in man have not been reported for these two drugs.

Robin and associates[16] using 0.1 mg. per kilogram of propranolol given intravenously to normal patients (slightly less than one third the average dose of sotalol given to our resting patients) report a 9 per cent decrease in heart rate (cf. 15 per cent decrease with sotalol), 2 per cent decrease in mean aortic pressure (cf. 3 per cent increase with sotalol), 21 per cent decrease in dP/dt (cf. 16 per cent decrease with sotalol), 31 per cent decrease in cardiac index (cf. 17 per cent decrease with sotalol), a 22 per cent decrease in stroke index (no change with sotalol), and a 10 per cent increase in LVEDP (cf. 20 per cent increase with sotalol). They report similar changes in a group of patients with coronary disease except that the LVEDP increased markedly with propranolol (197 per cent). Although these are not comparable groups of patients, propranolol seems to have less negative chronotropic effect and perhaps more negative inotropic effect as measured by decrease in stroke volume and rise in LVEDP in the coronary group (but not by dP/dt in both normal and coronary groups and LVEDP in normal group).

Parker and associates[17] report somewhat similar results using 0.15 mg. per kilogram of propranolol given intravenously in a group of patients with coronary disease. The decrease in cardiac index was about the same as in our patients (20 per cent decrease in patients with angina and 16 per cent decrease in those without); the change in stroke index was negligible. However, LVEDP rose somewhat more than in our study (63 per cent increase in angina group, 31 per cent in nonangina group).

The hemodynamic findings of Lewis and associates,[18] who used 10 mg. of propranolol given intravenously to 9 patients with coronary disease, are remarkably similar to our results with sotalol. The decrease in cardiac output was 20 per cent, with a small change in stroke index (9 per cent decrease). LVEDP increased 24 per cent and dP/dt decreased 27 per cent. Heart rate decreased 15 per cent. The results of Dwyer and associates,[19] who used 10 mg. of propranolol intravenously in 9 patients with coronary disease, are similar to ours with sotalol. Cardiac index fell 14 per cent and stroke index only 10 per cent. LV dP/dt fell 20 per cent, but there was no change in LVEDP.

The study by Hamer and Fleming[21] of 6 patients with aortic stenosis, in whom the ventricular rate after 5 mg. of intravenous propranolol was actually increased an average of 6 per cent over initial control values by atropine, can be compared with our study of fixed rate right ventricular pacing. They report a 14 per cent decrease in cardiac output (20 per cent decrease in our study), 20 per cent decrease in stroke volume (21 per cent decrease in our study), and a 7 per cent decrease in LVEDP (17 per cent increase in ours). Thus, the depressant effect of an average dose of 0.41 mg. per kilogram of sotalol is actually greater than that of 5 mg. of propranolol (approximately 0.07 mg. per kilogram, assuming a body weight of 70 kilograms) when the heart rate is maintained constant.

Donoso and associates[22] in a study of 9 elderly patients with fixed rate pacemakers reported a 16 per cent decrease in cardiac index and a 20 per cent decrease in brachial artery dP/dt after 0.1 mg. per kilogram of propranolol.

Thus, in this indirect type of comparison it appears that, when doses of propranolol and sotalol of relatively equal beta-adrenergic blocking potency (three to five times as much sotalol, weight for weight) are used, both drugs have significant negative inotropic effects in man separate from the negative chronotropic effect. It appears that propranolol may be slightly more depressant, although a final determination will have to await direct comparison of both drugs in the same study. In animals, propranolol is less depressant than sotalol,[2,4] but definite depressant effects of sotalol have been demonstrated.[5,8,24]

Sotalol is a less potent beta-adrenergic blocking agent than propranolol, does not block ouabain-induced arrhythmias as does propranolol,[4] and does have some negative inotropic effect in man. The significance of the latter in the clinical situation in man requires further observation.

Summary

The hemodynamic effects of sotalol (MJ 1999) were studied during diagnostic catheterization in 24 adult male patients at

rest, during exercise, and during constant rate right ventricular pacing. The depression in cardiac index at rest and during exercise appears to be secondary to the negative chronotropic effect of the drug since there was no change in stroke volume. The change in dP/dt and left ventricular end-diastolic pressure may also be a function of slowing of the heart rate. However with heart rate maintained constant by right ventricular pacing there was significant depression of cardiac function as indicated by a decrease in cardiac index, stroke index, and dP/dt and increase in arteriovenous oxygen difference. Sotalol appears to have both a significant negative chronotropic and negative inotropic effect in man.

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Pulse wave velocity in healthy subjects and in patients with various disease states

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Despite extensive studies on the velocity of the arterial pulse wave, there still seems to be a lack of agreement on the relative importance of various factors affecting its regulation. Early investigations on the relationship between pulse wave velocity (PWV) and pressure, tension, distensibility, and tube volume were made on excised segments of carotid arteries[1] and on cadaver aortas.[2] Factors that were believed to influence PWV include the degree of contraction of the smooth muscle,[3] the elasticity of the arterial wall,[4] the diastolic pressure,[5] the wall thickness,[4,6] the tortuosity of the vessel,[6,7] the diastolic vessel diameter,[4] the density of the blood,[4] and the velocity of the blood flow.[4]

In the intact human subject, however, the situation is more complex. There seems to be unanimous agreement that PWV increases with age, probably because of the physiologic stiffening of the arterial wall.[8-11] Children under the age of 10 years, however, have been shown to have a PWV faster than that of subjects aged 10 to 39 and equal to that of subjects aged 40 to 79 years.[15] The difficulty in separating the effect of aging from that of atheromatosis has led to conflicting reports on the influence of the latter on PWV. The finding of an increased velocity in patients with coronary artery disease[13] and in potential[14] and frank[14] diabetics has been interpreted as an indication of the presence of peripheral atheromatosis. On the other hand, Widmer,[18] who estimated PWV in 54 patients with definite arteriographic nonstenosing lower extremity atheromatosis, found values which were not different from those expected according to age and blood pressure. Normal PWV in patients with peripheral arteriosclerosis was also reported by Haynes and associates.[16] Patients with advanced arteriosclerotic peripheral vascular disease, however, have been reported to have a decreased PWV.[15,16,18]

Hypertension has been controversially reported to increase[16,17,7,19,22] or to have no influence[7,15,16] on PWV. Valvular lesions have, in general, been claimed to exert no effect on PWV.[23,24] Nevertheless, patients with aortic stenosis have been found to have increased values,[15] while those of patients with coarctation of the aorta are

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decreased.[11,13] Early studies have also suggested that heart rate,[13,14,17] exercise,[13] and cardiac arrhythmias[13,18] have no effect on PWV.

Some of the discrepancies mentioned above may have been due to inappropriate and different techniques. Thus, PWV has been variously estimated by measurements of the time intervals between the onset of the QRS complex and the onset of a peripheral pulse wave, or of the time intervals between two peripheral pulse waves. These are obviously not comparable, since the former includes time consumed for intracardiac events. Small samples of patients as well as difficulties in discriminating the effect of various factors represent additional obstacles to the drawing of comparable conclusions.

The purpose of this report is to present our experience with PWV in a total of 304 subjects. A noninvasive photoplethysmographic technique was used and two types of measurements were performed: one from the QRS complex to a peripheral pulse wave and the second between two peripheral pulse waves. The results may clarify some of the discrepancies that appear in the literature.

Material and methods

Arterial pulse waves were recorded by two noninvasive photoplethysmographic transducers of the reflecting type where photodetector and light source are placed side by side. One transducer was mounted over the femoral artery at the inguinal area, while the second was placed over the dorsalis pedis artery. With the patient in the supine position, recording was made on a Beckman direct writer five to ten minutes after positioning the transducer to allow for temperature equilibration of the photoconductive cells. The propagation time of the arterial pulse wave was obtained by measuring the time delay between the "feet" of two consecutive pulse waves, one recorded by the proximal and the other by the distal transducer at a paper speed of 250 mm. per second. The "foot" of the pulse wave is easily identified as a geometrical minimum at the onset of the wave and was chosen for corresponding measurements because its position is stable and almost invariable.[19] The interval $\Delta t(f\text{-}f)$ therefore, expresses the time required for propagation of the pulse wave from the femoral to the dorsalis pedis artery (in milliseconds). Simultaneous recording of the electrocardiogram (ECG) permitted measurement of the time interval between the peak of the R wave of the QRS complex and the foot of the femoral or the dorsalis pedis artery, $\Delta t(R\text{-}f)$. A constant of 50 msec. was subtracted from $\Delta t(R\text{-}f)$ in order to compensate for the isovolumetric contraction time. Pulse wave velocity (PWV) was then calculated by the formula: $PWV = L/\Delta t(f\text{-}f)$ where L = the length of the arterial segment between the two sites as determined by external measurements and by the formula: $PWV = L/[\Delta t(R\text{-}f) - 50 \text{ msec.}]$ where L was the distance between the third left parasternal intercostal space and the peripheral site (femoral or dorsalis pedis arteries).

A total of 304 male subjects were examined. Their distribution by diagnosis and age is given in Table II. The following terms were defined as indicated: hypertension, a blood pressure of 160/100 mm. Hg or more; ischemic heart disease (IHD), clinical and electrocardiographic evidence of angina pectoris or state after myocardial infarction; rheumatic heart disease (RHD), definitely proved mitral and/or aortic lesions; congestive heart failure (CHF), definite clinical evidence and a venous pressure of 12 cm. saline or more; diabetes mellitus, patients known to have the disease and to be receiving treatment for it; peripheral vascular disease (PVD), patients with intermittent claudication or with other definite clinical and/or angiographic evidence (33 patients had peripheral arteriosclerosis, and two had Buerger's disease); anemia, a hemoglobin level of 10 Gm. per cent or less (due to various causes). The patients were all afebrile and had not received vasodilators or beta blockers for at least one day prior to the examination. Some patients were receiving maintenance digitalis therapy.

The effect of a changing pulse rate on PWV was examined in eight subjects with persistent A-V block (third degree in six, and second degree in two) who were being treated by external transvenous pace-

Table I Reliability of method for measurement of pulse wave velocity (V)

	V(f-f)	V(R-f fem.)	V(R-f d.p.)
A Mean velocity (M./sec.) (84 measurements in 21 subjects)	10.6	3.4	6.3
B Variance among examined subjects (M./sec.)* (based on mean of 4 measurements)	3.50 (17.7)	0.64 (23.6)	1.04 (16.2)
C. Variance of repeat examinations (M./sec.)* (mean of 21 subjects)	1.66 (12.2)	0.05 (6.9)	0.12 (5.5)
D Ratio of variance of repeat examinations (C) to variance among subjects (B) (%)	47	7.8	11.5

*Coefficient of variation in brackets.

makers with catheter electrodes situated in the right ventricle. In five patients the PWV was examined during the slow spontaneous A-V nodal rhythm and again during pacing at a fixed rate of about 75 beats per minute. In four patients measurements were made during pacing at rates varying between a minimum of 48 to 67 and a maximum of 103 to 156 per minute. The effect of cardiac arrhythmias on PWV was examined by beat-to-beat measurements made on 40 to 50 cardiac cycles in patients with atrial fibrillation due to RHD (six cases) or IHD (three cases). In addition PWV generated by premature beats was examined by comparative measurements for premature and sinus beats in two patients with ventricular and in two with supraventricular premature beats.

In cases of heart block and arrhythmias where beat-to-beat comparisons were made in the same subject, the time intervals measured were $\Delta t(f\text{-}f)$ and $\Delta t(Q\text{-}f)$ where Q indicates the earliest deflection of the QRS complex. The latter was chosen instead of the $\Delta t(R\text{-}f)$ interval since the actual velocity did not have to be estimated.

Results

Reliability of method for measurement of pulse wave velocity. Twenty-one healthy subjects of various age groups were examined four times each on consecutive days, and the results are summarized in Table I. It may be seen from the table that the variance among repeat examinations in the same individual was greatest for measurements between the femoral and the dorsalis pedis arteries [$V(f\text{-}f)$] and smallest for measurements between the R wave of the electrocardiogram and the femoral artery [$V(R\text{-}f\ fem.)$]. The probable reason for this is that the peripheral arterial segment examined by measurements of $V(f\text{-}f)$ is most exposed to physiologic changes. The use of two photoplethysmographic transducers in measurement of $V(f\text{-}f)$ may also introduce an additional error. Nevertheless, even in $V(f\text{-}f)$ measurements, the ratio of variance of repeat examinations to variance among examined subjects is less than 50 per cent and may therefore be considered as relatively satisfactory. This ratio was much lower for $V(R\text{-}f)$ and therefore velocity measurements from the ECG to a peripheral pulse wave are more reliable.

Effect of age on pulse wave velocity. The results are summarized in Tables II and III. It may be seen from Table II that in healthy subjects the PWV increased steadily and significantly with age (from a mean of 9.4 M./sec. in the second to 11.4 M./sec. in the seventh decade and thereafter, $p < 0.001$). A similar increase in PWV with age was also detected in patients with hypertension without IHD (Group 2), although when these were added to a group of hypertensives with IHD the correlation with age was not significant. Neither could any significant correlation be detected in any of the other groups, possibly because of the relatively small numbers of cases and the paucity of younger subjects.

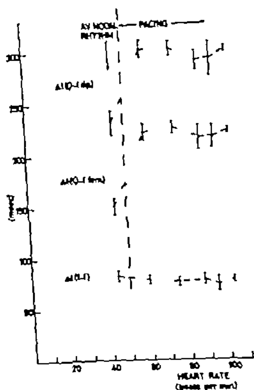


Fig. 1. Relationship between pulse rate and PWV as measured between the feet of the pulse waves of femoral and dorsalis pedis arteries, Δt(f-f), and between the Q wave of the ECG and peripheral artery Δt(Q-f), in patient with complete heart block, before and after pacing at different rates. Note no change in Δt(f-f) and lengthening of Δt(Q-f) by pacing. Δt(Q-f) shows no further change when the pacing rate is increased.

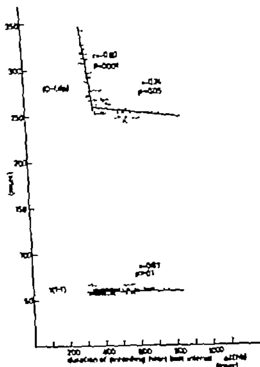


Fig. 2. Relationship between the duration of the preceding heart beat interval and PWV in case with atrial fibrillation. Note that there was no change of velocity as measured by Δt(f-f). On the other hand, an inverse correlation between Δt(Q-f) and Δt(hh) especially in the range of the shorter cycles, is present.

Similar relationships were found in the analysis of PWV as determined by the time interval Δt(R f) (Table III). Here a significant increase in PWV with age was detected in healthy individuals, as well as in patients with hypertension RHD and CHF

Effect of disease on pulse wave velocity When the effect of various diseases on PWV was examined in each age group it was evident that the most significant change occurred in patients with PVD who had a significantly slower PWV (Tables II and III). Hypertension had no significant effect below the age of 60 but increased PWV was found after this age. Two young subjects with diabetes had unusually high PWV's but no statistical evaluation was possible because of the small number of cases (Table II) The PWV in patients with IHD RHD or CHF was somewhat slower than that in healthy subjects in the same age group but the differences were not statistically significant.

Effect of heart rate on pulse wave velocity In patients with A V block the PWV as determined by the time interval Δt(f-f) showed no significant change when values during spontaneous rate were compared with values during pacing at a fixed rate of 60 per minute or at increasing fixed rates. This was true for all cases. An illustrative example is given in Fig 1. The time interval Δt(Q-f) however rose significantly with pacing although no further change was observed when the pacing rate was gradually increased. It may therefore be assumed that the prolongation of Δt(Q-f) was not due to a change in the propagation time of the pulse wave but to a lengthening of the left ventricular tension period (see Discu

Table II. Pulse wave velocity (V) as measured between the "feet" of the femoral and dorsal

Group	Patients	No.	11–20			21–30			31–40		
			No.	V	SD	No.	V	SD	No.	V	SD
1	Healthy subjects	105	21	9 4	1	16	9 7	1 2	25	10 2	1 3
2	Hypertension without IHD	1									
3	Hypertension with or without IHD	32									
4	IHD without hypertension	50									
5	RHD	15	1	6 7		1	9 5		5	10 1	6
6	CHF	40	1	10 5						12 5	
7	IVD	38				1	5 4		2	5 7	
8	Diabetes mellitus	26	1	6 4		1	13 8		2	13 3	
9	Anemia	18	1	9 4		1	11 7		1	11 7	

*Group 3 includes 21 patients from Group 2. Group 5 includes 5 patients also included in Group 6. Group 8 includes 12 patients a
†b. Regression coefficient; correlation coefficient; t. Student t distribution.
‡p < 0.01
§p < 0.05

sion). Furthermore, the latter was not due to a change in pacing rate but rather to the ectopic site of stimulation.

Effect of arrhythmia on pulse wave velocity. In eight out of nine cases with atrial fibrillation, the PWV as measured by $\Delta t(f\text{-}f)$ did not change significantly in spite of the large and random variation in cardiac cycle length (Fig. 2). In one case $\Delta t(f\text{-}f)$ showed a slight though significant tendency to increase with increasing preceding cycle length. The latter observation was confirmed when the patient was re-examined four months later. $\Delta t(Q\text{-}f)$ was, however, significantly inversely related to the duration of the preceding cycle length in all cases, especially in the range of the shorter cycles (up to about 750 msec.). Here again it may be assumed that alterations in $\Delta t(Q\text{-}f)$ were due to changes in the left ventricular tension period and not in the propagation time of the pulse wave.

In two cases, supraventricular premature beats generated a more rapid PWV than sinus beats [$\Delta t(f\text{-}f)$ = 80 and 102 msec., respectively]. On the other hand, in two other cases the PWV of ventricular premature beats as measured by $\Delta t(f\text{-}f)$ was equal to that of the sinus and postpremature beats (Fig. 3). The time interval $\Delta t(Q\text{-}f)$, however, was longer for both supraventricular and ventricular premature beats, intermediate for sinus beats, and shortest for postpremature beats (Fig. 3). A significant inverse correlation was found between $\Delta t(Q\text{-}f)$ and the preceding cycle length. It may be concluded that premature beats generated longer $\Delta t(Q\text{-}f)$ intervals because of longer left ventricular tension periods, while the propagation time of the pulse wave was unchanged (in ventricular premature beats) or even increased (in supraventricular premature beats).

Discussion

The results of the present study are in agreement with previous observations that PWV increases with age,[17] probably because of loss of arterial elasticity due to the process of aging.[19,20] It is worth noting that the PWV of subjects aged 60 years or more was slower than that of subjects aged 51 to 60 years. This is in keeping with ob

...e waves [V (f f)] in healthy subjects and in patients with various diseases

		51–60			>60			Correlation with age			
V	S.D	No.	V	S.D	No.	V	S.D	b†	r	t	p
1 3	1 8	10	12 8	3 6	16	11 4	1 7	+0 048	+0 43	4 79	<0 001
3 0	2 5	7	12 7	2 9	6	15 7‡	3 8	+0 131	+0 51	2 58	<0 02
13 0	2 5	11	12 6	2 8	13	13 4	3 6	+0 066	+0 23	1 30	>0 1
10 8	1 7	14	11 2	2 2	30	10 7	1 7	−0 021	−0 11	0 73	>0 1
10 2	1 0	4	9 8	2 8				+0 035	+0 17	0 62	>0 1
9 2		13	10 8	2 8	22	10 7	2 1	+0 042	+0 27	1 73	<0 1
7 3‡	1 7	5	8 1‡	2 0	25	6 7‡	1 3	−0 017	−0 18	1 11	>0 1
11 1		4	11 2	2 9	17	11 7	1 8	+0 005	+0 03	0 17	>0 1
12 2		4	11 3	1 2	10	12 1	3 6	−0 020	−0 12	0 48	>0 1

...n Groups and 6.

...ervations by Bramwell and Woolam and associates that the rate of increase of the PWV was smaller in the higher age groups. It is possible that undiagnosed stenosing atheromatosis, which is more prevalent in older individuals, may have an effect opposite to that of age. As may be seen from Tables II and III advanced PVD leads to a slowing of PWV in all age groups.

The observations reported above may throw some light on the yet unresolved discussion concerning the relationship between PWV and arterial blood pressure. Theoretical considerations suggest that an increase in PWV should be expected with increasing blood pressure.[30] In situ experiments seem to indicate that the arteries exhibit a nonlinear stress-strain relationship even at the different pressure levels occurring during a normal cardiac cycle.[31-33] The propagation velocity of pulsation superimposed on the arterial wall by external impact generators has been found to increase during systole and decrease during diastole.[33] The results of these studies are, however subject to criticism because the frequency content of the impact waves (70 to 120 Hz.)[33] is considerably higher than that of the arterial pulse wave. Furthermore, it is very probable that the frequent periodic "knocking" of the artery activates the smooth muscle thus changing the mechanical properties of the arterial wall.

In vivo measurements reported by other workers show that the strain-stress relationship in the arterial wall during a normal cardiac cycle is nearly constant[34,35] and that nonlinearities, whenever present, are small and negligible, especially at lower pressures.[35,36]

Our results indicate that the blood pressure level in itself has no effect on the velocity of the pulse wave. This conclusion is demonstrated by the fact that the average values for 31 hypertensive subjects were similar to those of normotensive subjects except in the oldest age group. Furthermore, large beat-to-beat variations in diastolic pressure in cases of atrial fibrillation and premature ventricular beats, as well as significant blood pressure changes induced by cardiac pacing at increasing rates, had no effect on PWV as measured between two peripheral sites. It is important to

Table III. Pulse wave velocity (V) as measured between the R wave of the ECG and the foot of

Group	Patients	No.	Ap								
			11-20			21-30			31-40		
			No	V	S.D	No	V	S.D	No	V	S.D.
1	Healthy subjects	105	21	5 5	0 6	16	5 7	0 6	25	6 2	0.5
2	Hypertension without IHD	21									
3	Hypertension with or without IHD	32									
4	IHD without hypertension	47									
5	RHD	15	1	4 1		1	5 5		5	5 8	0 6
6	CHF	37	1	5 7					2	6 1	
7	LVD	37				1	4 1		2	4 2	
8	Diabetes mellitus	23	1	4 5		1	5 5		2	7 2	
9	Anemia	18	1	5 9		1	6 6		1	8 3	

Group 3 includes 21 patients from Group 2; Group 5 includes 5 patients also included in Group 6; Group 8 includes 12 patients als
†k, Regression coefficient   correlation coefficient t, Student t distribution.
‡p < 0.01
§p < 0.01.

stress that the pressure changes occurring during atrial fibrillation premature beats and cardiac pacing at different rates are due to alterations in cardiac output rather than peripheral resistance It is therefore not surprising that PWV was, in these cases, not related to the changes in blood pressure.

These findings agree with those reported by some authors[7,13,14] and seem to indicate that the increase in PWV in hypertensive subjects reported by other investigators[10,13,17,18,23] is due to an accelerated aging of the arterial wall rather than to the blood pressure level itself This view is further supported by the finding of Nielsen and colleagues[17] that PWV is correlated to the systolic pressure only which as is well known rises with age as a result of loss of arterial elasticity

A comparison of measurements of PWV from the Q wave to a peripheral site on one hand and between two peripheral sites on the other shows that in arrhythmias and in cardiac pacing these measurements behave in a totally different manner The reason for this is that the time interval $\Delta t(Q\text{–}f)$ is composed of two periods related to different physiologic events (1) the tension period of the left ventricle $\Delta t(tp)$ and (2) the propagation time of the pulse wave from the root of the aorta to a peripheral site $\Delta t(a\text{–}f)$ Therefore $\Delta t(Q\text{–}f) = \Delta t(tp) + \Delta t(a\text{–}f)$ Although $\Delta t(a\text{–}f)$ was not measured directly in this study its changes are reflected in measurements of $\Delta t(f\text{–}f)$ It may therefore be concluded that changes in $\Delta t(Q\text{–}f)$ in the presence of a constant $\Delta t(f\text{–}f)$ are due to variations in the left ventricular tension period Hence a prolongation of $\Delta t(Q\ f)$ of beats with shorter preceding cycle lengths in atrial fibrillation premature beats and during cardiac pacing may be interpreted as an indication of a prolonged left ventricular tension period It is interesting to note that $\Delta t(Q\ f)$ was prolonged by pacing induced by right ventricular stimulation but no additional change occurred after increasing the pacemaker rate It may therefore be concluded that the increase in left ventricular tension period was due to a slower spread of ventricular excitation during pacing[17]

An additional finding in this study was

lorsalis pedis pulse wave [V(R–f.d p)] in healthy subjects and in patients with various diseases

p									*Correlation with age*			
41 50			*51–60*			*>60*						
.	V	S.D	No.	V	S.D	No.	V	S.D	H	r	t	p
7	6 5	0 9	10	7 2	1 3	16	7 2	0 8	+0 028	+0 49	3 70	<0 001
8	7 4	1 6	7	7 4	0 7	6	9 0†	1 7	+0 070	+0 49	2 45	<0 05
8	7 4	1 6	11	7 4	0 6	13	7 8	1 7	+0 031	+0 24	1 35	>0 1
6	6 5	0 9	14	7 0	0 8	27	6 8	1 2	0 000	0 00	0	>0 1
4	5 9	0 6	4	6 0	1 3				+0 053	+0 66	3 17	<0 01
2	6 0		12	6 4	1 0	20	6 5	1 6	+0 037	+0 40	2 60	<0 02
5	5 0‡	1 0	5	6 6	1 8	24	5 3‡	0 8	+0 007	+0 10	0 61	>0 1
1	5 9		4	7 2	0 7	14	7 6	1 5	+0 021	+0 24	1 13	>0 1
1	6 6		4	7 2	1 3	10	7 4	1 1	+0 020	+0 30	1 26	>0 1

cluded in Groups 4 and 6.

the lack of dependence of the PWV on heart disease. Thus, the average values in patients with ischemic or rheumatic heart disease, as well as in patients with heart failure were not statistically different from those of healthy subjects On the other hand pacemaker-induced tachycardia and anemia which lead to increased cardiac output and rapid circulation time also had no effect on PWV The finding of no significant change of PWV in 50 normotensive patients with ischemic heart disease is at variance with results reported by Simonson and Nakagawa[12] in 42 similar patients, but in agreement with the finding of McLean and co-workers.[21] The former group used impedance plethysmography and measured the time interval between the feet of the aortic and the femoral pulses, while the latter estimated the time interval between the Q wave and the foot of the brachial artery pulse. It is not clear whether the differences in results are due to methodology or to different patient sampling

Our findings indicate unequivocally that while the process of aging is accompanied by an increase in PWV stenosing peripheral vascular disease leads to decreased PWV The latter finding is in keeping with previous reports.[13,17,20] The effect of peripheral arterial stiffening on PWV is probably dependent on its extent and degree. Mild arteriosclerosis may have no effect or an effect similar to that of aging while advanced stenosing atheromatosis may decrease PWV because of diversion of blood to smaller collateral vessels.[13] It is probable therefore that some of the discrepancies on this subject[12,14 1-11] are due to patient sampling

Summary

Pulse wave velocity (PWV) was determined in 105 healthy subjects and in 199 patients suffering from eight different pathologic states. A noninvasive photoplethysmographic technique was used and two time periods were measured (1) between the "feet" of the pulse waves of the femoral and the dorsalis pedis arteries and (2) between the QRS complex and the pulse wave of the dorsalis pedis artery

PWV was found to increase significantly with age. Hypertension was accompanied

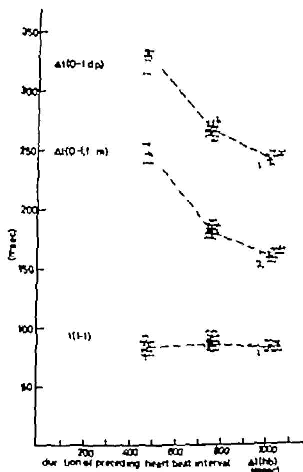


Fig. 3. PWV generated by premature ventricular beats, sinus beats and postpremature beats. Note that Δt(f-f) remain constant for all beats while Δt(Q-f) is longest for premature beat (left), intermediate for sinus (middle) and shortest for post premature beat (right).

by increased PWV only in older subjects, while peripheral vascular disease was associated with decreased PWV. No significant change was observed in normotensive subjects suffering from ischemic heart disease, rheumatic heart disease, congestive heart failure, diabetes mellitus or anemia.

The time interval between the feet of the femoralis and dorsalis pedis arteries Δt(f-f) was not altered significantly by cardiac pacing at a fixed and at increasing heart rates in eight patients with A-V block. Beat to beat measurements in eight cases of chronic atrial fibrillation showed that Δt(f-f) was constant and independent of the preceding cycle length and therefore of variations in blood pressure. Premature beats generated Δt(f-f) s which were equal to or shorter than those generated by sinus or postpremature beats.

On the other hand, the interval between the Q wave of the ECG and the foot of the pulse wave of the dorsalis pedis artery Δt(Q-f d.p.) was prolonged by cardiac pacing and was inversely related to the preceding cycle length in atrial fibrillation. Likewise Δt(Q-f d.p.)s generated by premature beats were longer than those of sinus and postpremature beats. This finding is interpreted as indicating a prolongation of the left ventricular tension period rather than a change in the propagation time of the pulse wave.

The difference in behavior of the two time intervals mentioned above should be taken into consideration in measurements of PWV.

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Cigarette smoke Effects on lactate extraction in the presence of severe coronary atherosclerosis

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Epidemiologic studies have demonstrated a significant relationship between cigarette smoking and obliterative vascular disease[1] Of clinical importance is the significant relationship between cigarette smoking myocardial infarction and sudden death Several studies[2-4] show an increase in deaths from coronary disease in cigarette smokers.

The objectives of this study were to determine whether the inhalation of cigarette smoke could acutely induce myocardial ischemia as reflected by abnormal myocardial lactate metabolism in patients with severe diffuse obstructive coronary artery disease to compare this situation to the effects of catecholamine administration and to measure some of the hemodynamic responses to the inhalation of cigarette smoke

Methods and materials

Fifteen patients aged 37 to 65 years with severe angina pectoris were the study subjects Selective coronary angiography[8] was performed in all subjects and revealed 75 per cent to total obstruction in each of two or three major coronary vessels following the administration of sublingual nitroglycerine. Each subject had smoked cigarettes for at least 10 years in the quantity of 20 to 50 cigarettes daily Eleven patients were men 4 were women

Pressure and time indices in the cardiac chambers and great vessels were measured and calculated with the use of standard techniques.[9,10] The coronary sinus was catheterized with a No 7 Cournand or Goodale Lubin catheter and blood samples for lactate level determination were drawn simultaneously from the coronary sinus and aorta and sequentially in the distal mid and proximal coronary sinus positions. Lactate levels were determined by the enzymatic conversion of this substrate to pyruvate yielding reduced nicotinamide adenine dinucleotide (NAD) The quantity of NADH was then determined spectrophotometrically[11] Determinations were made at rest during the inhalation of cigarette smoke and during the administration of isoproterenol 2 γ per minute Lactate extraction or production was calculated with the formula $\frac{A - V}{A} \times 100 =$ per

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cent lactate extraction The distal, mid and proximal coronary sinus sampling sites were considered to drain the anterior lateral and posterior left ventricular myocardium respectively [11]

During the smoking state each patient smoked 2 regular commercial cigarettes for a total of 8 to 10 minutes, averaging 6 puffs per minute, and inhaling following each puff Blood samples for lactate studies were drawn and pressure and time indices measured during the last 30 seconds of smoking During isoproterenol infusion blood samples were drawn when a sustained increment in heart rate of 50 per cent was measured for 5 minutes.

Results

Heart rate (Fig 1) increased by an average of 16 per cent in 13 of 15 patients during cigarette smoking The average heart rate in the control state was 78 beats per minute and rose to 88 beats per minute during smoking The range of increasing rate was 3 to 56 beats per minute. In 2 patients there was slowing of 2 and 7 beats per minute.

Systolic ejection periods and diastolic filling periods per beat were within normal limits when corrected for heart rate and remained within these limits during the control and smoking periods. When calculated as the systolic ejection period and diastolic filling period per minute these changes were +12 per cent and −8 per cent, respectively

Mean aortic pressure (Fig 2) increased by an average of 14 per cent in 13 of 15 patients. The average control pressure was 87 mm Hg and rose to an average of 98 mm. Hg during smoking The range of increase was 3 to 41 mm. Hg In 2 patients reduction of 10 and 9 mm Hg occurred.

The aortic mean systolic pressure increased by an average of 10 per cent in 13 of 15 patients. The average aortic mean systolic pressure was 114 mm. Hg during the control period and 126 mm Hg during smoking in 13 patients. In 2 patients reductions of 15 and 18 mm Hg occurred. The aortic mean diastolic pressure increased by an average of 10 per cent in 13 patients. In the control period the average mean diastolic pressure was 73 mm. Hg rising to

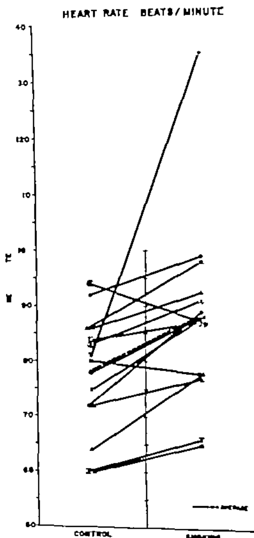


Fig. 1 Heart rate during the control state and the smoking state in 15 patients. Average values are connected by the broken line.

80 mm Hg during smoking In 2 patients a reduction of 10 and 7 mm. Hg occurred

The tension-time index per beat (pressure time index) (Table I) averaged 31.8 mm Hg second (sec) per beat during the control state and 32 6 mm. Hg sec per beat during smoking The range of changes was −32 per cent to +23 per cent. Eight of 15 cases varied by less than ±10 per cent and 12 of 15 cases varied by less than ±20 per cent from the control state In creases were noted in 13 of 15 cases.

When calculated as the tension time index per minute (Table I) control values averaged 2 472 mm. Hg sec per minute

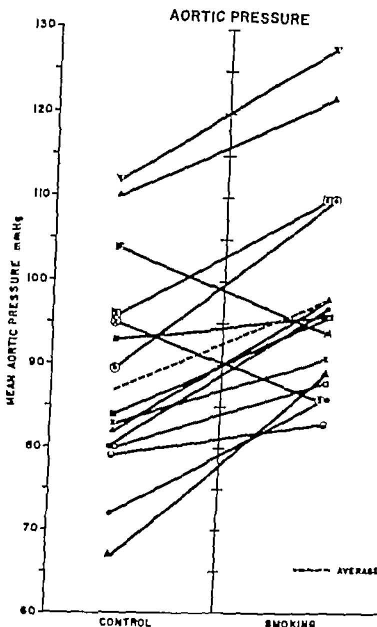


Fig 2 Mean aortic pressure during the control state and the smoking state in 15 patients. Average values are connected by the broken line

and 2 747 5 mm Hg sec per minute during smoking The average increase was +11 per cent The range of change was −12 per cent to +37 per cent Five varied less than ±10 per cent Increases were noted in 13 of 15 cases The increase from the control to the smoking state had a significance of $p < 0.001$

Arterial lactate levels were 0 3 to 1 3 mM per liter Changes between the control and smoking state were less than 5 per cent and between smoking and isoproterenol administration were elevated by an average of 15 per cent.

Percentage myocardial lactate extraction during the control period (Fig 3) exceeded 10 per cent at all sampling sites in 12 of 15 patients In 2 patients lesser degrees of lactate extraction were found at one site and in one patient lactate production at one site was found together with diminished extraction in another site

During the smoking period (Fig 4) 12 patients extracted lactate at all sampling sites. These were the same 12 patients who had this finding during the control state One patient with lactate extraction of less than 10 per cent at one site during the control developed diminished extraction at all 3 sampling sites.

During isoproterenol infusion (Fig 5) one patient had lactate extraction exceed

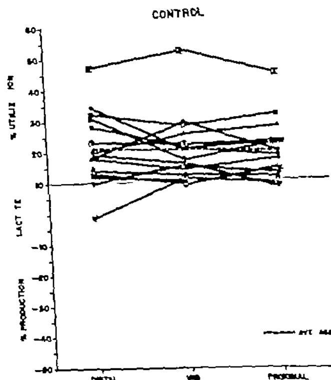


Fig. 3. Myocardial lactate metabolism in 15 patients during the control state at three coronary sinus drainage sites.

Table I. A comparison of myocardial lactate extraction and the tension-time index during the control period and during smoking

Patient	% lactate extraction (control)			Tension-time index per beat*-per minute† control		% lactate extraction (smoking)			Tension-time index per beat-per minute smoking	
	D‡	M‡	P‡			D	M	P		
1	18	29	19	30 4	2 401 6	17	21	26	20 5	2 767 5
2	34	24	18	36 4	3 146 8	25	19	20	42 9	4 118 4
3	−1	11	9	26 4	2 481 6	3	1	2	32 5	2 827 5
4	19	16	8	37 2	2 790	12	2	2	35 9	3 087 4
5	23	23	23	38 9	3 228 7	25	26	29	31 0	2 821
6	13	9	15	24 4	1 927 6	4	7	0	23 5	1 950 5
7	12	10	10	38 4	2 804	12	11	12	38 4	2 419 2
8	28	21	22	31 9	2 532	33	7	51	31 2	2 511 6
9	47	32	44	38 0	2 280	41	42	36	39 0	2 535
10	20	25	27	35 0	2 940	19	19	25	35 0	3 150
11	18	14	17	31 8	1 971 9	21	17	19	33 8	2 568 8
12	10	14	12	25 9	2 264 8	10	10	12	27 6	2 346
13	14	12	11	23 4	1 989	11	14	14	28 8	2 736
14	31	17	22	36 0	2 592	22	26	16	41 5	3 112 5
15	32	28	31	24 0	2 016	31	18	18	26 6	2 261
				Average 31 8	2 4 2				Average 32 6	2 747 5

*mm. Hg sec per beat.
†mm. Hg sec per minute.
‡Sampling sites: D, distal; M, mid; P, proximal coronary sinus.

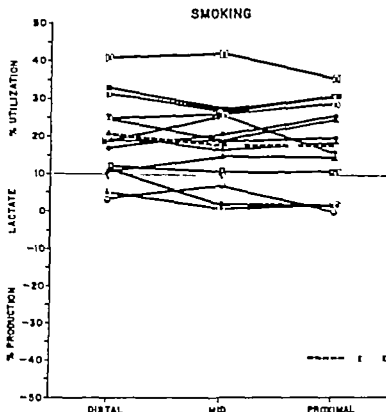


Fig 4 Myocardial lactate metabolism in 15 patients during the smoking state.

ing 10 per cent at 3 sampling sites and 11 patients had lactate production at each site Three patients had combinations of normal and diminished extraction or frank *production*

Average per cent extraction (Fig 6) was 21 20 and 19 per cent at the distal mid and proximal coronary sinus drainage sites respectively during the control state and 19 18 and 18 per cent at the same sites during smoking During isoproterenol in fusion lactate production of 5 15 and 12 per cent was found at the distal mid and proximal coronary sinus sampling sites respectively

Changes in heart rates between the con trol and smoking states in the three patients with diminished lactate extraction at rest were 94 to 87 (Patient 3) 75 to 88 (Pa tient 4) 78 to 88 (Patient 6) beats per minute Respective changes in mean aortic pressure were 69 to 110 83 to 91 and 79 to 83 mm Hg and changes in the tension time index per minute were 2 481 6 to 2 827 5 2 790 to 3 087 4 and 1 927 6 to 1 950.5 mm Hg sec per minute

Discussion

A statistically significant relationship between cigarette smoking and myocardial infarction and sudden death has been found in several epidemiological studies.[1-7] In con trast the relationship between cigarette smoking and angina pectoris has not been *found to be significant*

The combined experiences of the Albany and Framingham studies[7] reveal that angina pectoris is no more frequent in cigarette smokers than in nonsmokers. This suggests that acute hemodynamic changes induced by nicotine inhalation are inadequate to cause transient ischemia manifested as chest pain but may dispose to acute arrhythmias or those acute changes leading to myocardial necrosis.

Anginal pain precipated by cigarette smoking in a patient with clinically evident ischemic heart disease was infrequently found by White and Sharber[13] S T seg ment depression and T wave changes noted in electrocardiograms (ECG s) recorded during smoking have been reported by von Ahn[14] and Davis.[15] The absence of angina pectoris following a pharmacologic or hemodynamic intervention does not signify adequate myocardial oxygenation The presence of anaerobic myocardial metabolism[16] and transient ECG abnor malities associated with ischemia have been documented following myocardial stress in

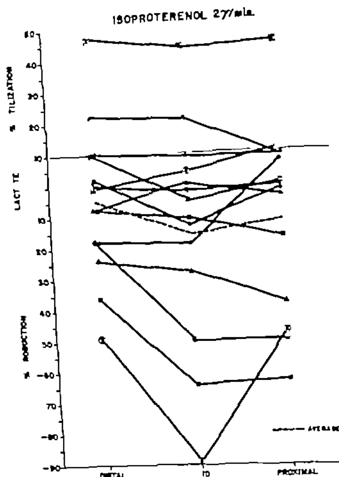


Fig. 5 Myocardial lactate metabolism in 14 patients during isoproterenol infusion.

the absence of clinical symptoms.[17] Turner and Morton found that one third of the patients with abnormal ECG s during the anoxemic test for coronary insufficiency had no chest pain Scheuer and Brachfeld have found that abnormalities in lactate metabolism may precede ECG changes in acutely induced ischemia. It was therefore of interest to determine whether the inhalation of cigarette smoke could induce myocardial ischemia which was not clinically detectable.

In animal experiments Forte and associates[19] and Kien and Sherrod[21] have found increasing coronary flow following cigarette smoke inhalation In rabbits with coronary atherosclerosis Travell Rinzler and Karp[22] found that intracoronary injection of nicotine decreased coronary blood flow During the initial period of reduced flow S-T segment depression occurred in the ECG Secondary increases in flow were not observed in the atherosclerotic hearts but occurred in the hearts of the normal group. Bellet, West, and Guzman[23] have demonstrated ECG changes in dogs with ligated coronary arteries at far lower doses of nicotine than needed to elicit the same changes in normal animals.

In clinically normal humans Bargeron and co-workers[24] found early increases in coronary flow with little change in myocardial oxygen consumption during cigarette smoking Heart rate increased and coronary vascular resistance decreased In addition there was a decline in the average myocardial lactate and pyruvate extraction but these changes were not statistically significant. Again it is to be remembered that these patients had no evidence of coronary atherosclerosis.

Increasing total coronary blood flow is l

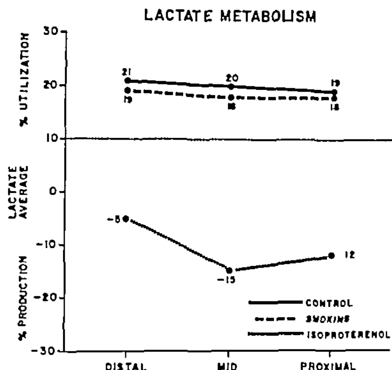


Fig. 6. Average myocardial lactate production or utilization in the control state, during smoking, and during isoproterenol infusion.

itself not evidence of increased oxygen supply to those areas having the greatest requirements. Currently available methods for measuring coronary blood flow in the intact human relate flow to muscle weight but do not determine flow distribution. To assess the regional adequacy of coronary flow during changes in myocardial oxygen requirements, the determination of myocardial lactate extraction and production was used.

The use of lactate extraction as an indicator of ischemia has several shortcomings. Blood lactate levels are only indirect reflections of mitochondrial redox potential. A consideration of myocardial distribution and diffusability of lactate is also pertinent to a consideration of the use of this method. Glaviano[26] demonstrated that myocardial lactate levels vary in different areas of the cardiac chamber walls. Herman, Elliott, and Gorlin[24] however, have found that lactate extraction by the myocardium is uniform. Glaviano's findings suggest that the passage of lactate into the myocardial cell is by active transport rather than by passive transfer, as was proposed by Huckabee.[27]

Further consideration of the sampling technique is required. Samples drawn within the coronary sinus represent a mixture of blood from various drainage sites. Small or localized changes in the lactate level may be lost due to dilution and mixing in the coronary sinus. In addition, the communication of the coronary sinus with the anterior cardinal veins may alter the direction of drainage and therefore the concentration of lactate at the sampling site.

Despite these difficulties, myocardial lactate production offers evidence of increased glycolysis, which in the presence of severe obstructive coronary disease can be assumed to be ischemic in origin. Acceptance of this condition allows for conclusions concerning the effects of any stressful intervention upon the relationship of myocardial oxygen need to supply. Sampling at multiple sites in the coronary sinus lessens the error due to mixing and allows a gross determination of the site of origin of the measured lactate.

Cohen and co-workers[22] and Carlsten and associates[23] have demonstrated lactate extraction at rest with increasing myocardial lactate utilization during stress in the presence of an adequate oxygen supply. Herman, Elliott, and Gorlin[24] found that patients with no coronary disease utilized

more than 10 per cent of arterial lactate at rest. During stress, myocardial lactate utilization usually increased but could also decrease to a normal limit of 10 per cent. Inhalation of cigarette smoke in man raised blood levels of free fatty acids.[39] Small decrements in lactate utilization may be explained by preferential uptake of free fatty acids.

The absence of lactate production during smoking must be further considered. It might mean that the hemodynamic changes induced were not sufficient to cause myocardial ischemia, or that the method used was insufficiently sensitive to determine this occurrence. It would seem that the former was more likely since clinical expression of ischemia in the form of angina pectoris is not more frequently associated with smoking and might be expected to be so if ischemia was produced. Another alternative would be that coronary blood flow was increased in these patients. Regan and associates[31] found no increase in coronary flow in subjects with coronary artery disease during smoking. Finally, nicotine might cause regional flow redistribution to the benefit of potentially underperfused areas. Evaluation of this possibility awaits the availability of methods for studying regional flow in the intact heart.

Inducing more rapid heart rates by atrial pacing or infusion of isoproterenol has been used to provoke myocardial ischemia. [32] Angina pectoris has been induced by increasing the resting heart rate by as little as 20 beats per minute.[33] The positive chronotropic effects of nicotine are at least partially the result of increasing blood catecholamine levels.[33] Despite intense cigarette smoking, heart rate increased by an average of only 10 beats per minute, a small and metabolically insignificant increment.

Roughgarden and Newman[35] have reviewed and tabulated many of the hemodynamic studies done on angina patients. When anginal pain occurred without an obvious precipitating cause, average increases in systolic pressure were 9 per cent above the baseline and average diastolic increases were also 29 per cent greater. The average increase in pulse rate was 30 per cent.

Angina pectoris occurring as a result of physical exertion was associated with a wide range (1 to 78 per cent) of systolic blood pressure elevation with an average increased value of 27 per cent. The average elevation of diastolic blood pressure was 23 per cent. Of interest is the fact that approximately one third of the patients had no change or a falling diastolic blood pressure.

Roughgarden's[34] own studies revealed average increases of 24 per cent in systolic pressures and 26 per cent in diastolic pressures. These values exceed the average changes for systolic and diastolic blood pressure as well as for heart rate found in this study. While angina did occur with relatively small changes in several patients reported by Roughgarden, we do not know the severity of the coronary artery disease in these individuals. In addition relaxation associated with cigarette smoking in the catheterization laboratory may have altered the perception of anginal pain.

Cohen and associates[37] have performed metabolic as well as hemodynamic studies during angina pectoris. Of particular interest was the presence of excess lactate in 88 per cent of patients when chest pain occurred and the lack of difference of heart rate and duration of the systolic ejection period when compared to nonanginal patients. In addition there was a less than normal increase in the systolic ejection rate and the cardiac output when angina occurred during exercise or isoproterenol infusion.

Regan and co-workers[38] found that cigarette smoking had no significant effect on myocardial and total body oxygen consumption in normal subjects and people with clinical evidence of coronary artery disease. In contrast, increases in heart rate, mean arterial pressure, and left ventricular work were significant in both groups. Of great interest was the absence of changes in myocardial oxygen consumption and coronary blood flow despite increase in heart rate, aortic pressure, and left ventricular work.

The product of the systolic ejection period and left ventricular mean systolic pressure has been expressed as the tension-time index.[39] Increases in this determinant

of myocardial oxygen need were calculated in 13 of 15 patients but only 3 of the 13 had abnormal lactate extraction The increase in the tension time index was statistically highly significant.

The tension time index is in fact a derived value which does not truly measure tension but rather the product of the duration of ejection and systolic pressure Levine and Wagman[33] have demonstrated that it is possible to calculate similar values in the presence of dissimilar left ventricular radii Nonetheless Neil and co-workers[37] and Rolett and co-workers[38] have demonstrated that this index permits reliable predictions of myocardial oxygen consumption

Increases in aortic pressure may be translated into increased afterload a determinant of left ventricular function and a factor influencing oxygen requirements[41] Again the increase in mean aortic pressure was small and ischemia was not induced in patients with prior aerobiasis

In each of the 3 patients who had abnormal lactate metabolism during the control period ischemia was made more diffuse and slightly more severe by smoking Small increases in heart rate mean aortic pressure pressure-time indices and diastolic filling period occurred in 2 patients In the third a reduction in heart rate (94 to 87 beats per minute) and an increase in mean aortic pressure (89 to 110 mm Hg) were found The tension time index in this patient increased by 23 per cent This suggests that during smoking small changes in factors influencing myocardial oxygen utilization may sustain and aggravate an already existent ischemia state

The production of lactate induced in 11 of 12 nonischemic hearts by the infusion of isoproterenol in modest amounts suggests the extreme severity of disease in these patients. A similar stress has been found to induce lactate production much less frequently in the presence of obstructive coronary disease[14,22] Indeed this adds to the significance of the lack of evidence of ischemia during the smoking period and suggests that this form of stress is of importance only in the presence of existent ischemia or even more severe coronary artery disease

Summary

Fifteen patients with angiographically demonstrated severe obstructive coronary artery disease were the study subjects. Hemodynamic measurements were made before and during cigarette smoking and metabolic evaluation was performed in these states and during isoproterenol stress. Heart rate aortic pressure systolic ejection and diastolic filling periods were measured. Myocardial lactate extraction was evaluated at three coronary sinus drainage sites. Despite increases in heart rate aortic pressure the systolic ejection period per minute and the tension time index per minute lactate production was not induced by smoking in any patient without lactate production in the control state. In 3 patients with lactate abnormalities prior to smoking inhalation of cigarette smoke sustained and slightly aggravated this circumstance Isoproterenol induced lactate production in all but 1 patient.

Cigarette smoking in a group of patients with severe obstructive coronary artery disease did not produce evidence of ischemia as determined by abnormalities in lactate extraction

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stenosis (1 subject) The ages were between 2 and 37 years. Twelve patients were men 2 were women.

The following ECG data were studied the P R duration ÂP and the polarity of the P wave in Leads I II III aVR, aVL, V and V6. In the VCG the duration of the P loop its rotation in the frontal, right sagittal and horizontal planes, and the direction of the initial limb (first vector) and of the greatest vector (i.e the highest voltage for any P loop) in the three planes were analyzed.

The VCG in the frontal right sagittal and horizontal planes were recorded separately with the Grishman system [1] with the use of the Sanborn Model 569 Viso Scope apparatus oscilloscopic patterns were photographed with a Voigtländer camera and redrawn at known amplification (Figs. 2 5) The electrical beam was interrupted 250 or 500 times per second. For the spatial calculus of the first and the greatest vectors the formula

$$Sv = \sqrt{x^2 + y^2 + z^2}$$

was used where *Sv* is the spatial vector and *x y* and *z* represent the transverse, vertical and sagittal components of that vector

Results

ECG findings (*Table I*) The P R interval was normal (≥0 12 second) in 10 subjects and shortened in 8 In one case the P wave was retrograde. In 9 of 10 subjects with a normal P R interval the duration did not exceed 0 13 second The mean electrical axis of the P wave was oriented between −50 and −120 degrees, with an average value of −68 degrees. In only one subject was the P wave oriented from left to right (−120 degrees) but it did not exhibit the VCG pattern of so-called left atrial rhythm. The P wave was negative in Leads II III and aVF In Lead I it was positive in 15 subjects, diphasic (+−) in 3 and negative in 1 (Case 861) In aV It was positive in all subjects, except 1 (Case 861) in whom it was negative In aVR the P wave was positive in 8 subjects, isoelectric in 7 diphasic (+−) in 3 and negative in 1 In V the P wave was positive i 6 cases, isoelectric in 2 diphasic (+−) in 7 diphasic (−+) in 3

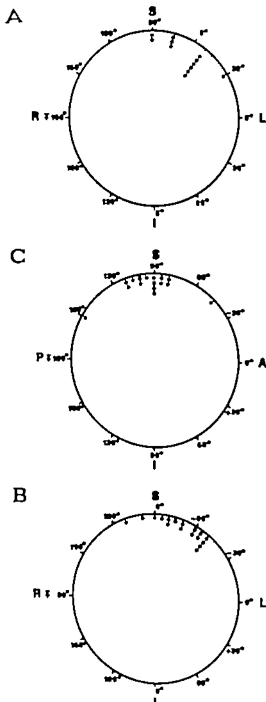


Fig. 1 Histograms of the direction of (*A*) the initial limb (first vector) of the P loop in the frontal plane of the greatest vector (highest voltage vector) in the (*B*) frontal and (*C*) sagittal plane in different cases of inferior atrial rhythm. *S* superior *I* inferior *P* posterior *A* anterior *L* left *R* right.

Inferior atrial rhythms

Vectorcardiographic study and electrophysiologic considerations

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Sergio Dalla Volta, M.D.
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The electrocardiographic diagnosis of inferior atrial rhythms (IAR) is based on the direction of the electrical axis of the P wave and on the chronologic relations between the P wave and the QRS complex. More specifically, in nodal and coronary sinus rhythms there is an upward and leftward deviation of ÂP. This is independent of the relationship between the P wave and the QRS complex occurring in so-called upper, middle, or lower nodal rhythms.

We are not aware of the existence of clinical vectorcardiographic studies of the P wave in these cases; this probably is because of technical difficulties and the lack of interest in an ectopic rhythm regarded by most to originate from a single location.

Recent electrophysiologic studies[1] have prompted a re-evaluation of the hypothesis of a nodal origin of these rhythms because A-V junctional nodal cells do not have automatic properties, which, in contrast, have been demonstrated in atrio-nodal, in nodal-His regions, and in other areas of the atria. These investigations, however, have not strictly defined the loci of origin of ectopic rhythms, the activation pathway in these rhythms, and the relations between IAR and A-V conduction.

Previous investigations from this institution[4-7] have shown the reliability of vectorcardiographic techniques to allow a detailed analysis of atrial vectors and for a closer correlation with recent electrophysiologic findings. Particularly, this technique, when compared with the electrocardiogram (ECG), permits a more accurate diagnosis of ectopic atrial rhythms.

Interest in the mechanism of IAR with special reference to the origin of the pacemaker from one or more points and to the acceptability of the classical distinction between nodal and coronary sinus rhythms, granted this study.

Material and methods

Nineteen vectorcardiograms (VCG's) in 18 cases of IAR diagnosed by the surface ECG (negative P waves in Leads II, III, and aV$_F$) have been analyzed. Five subjects were normal and in the other 13 the following clinical diagnoses were made: atrial septal defect (4 subjects), ventricular septal defect (3 subjects), cardiomyopathy of unknown etiology (2 subjects), hypertrophic infundibular subaortic stenosis (1 subject), endomyocardial fibroelastosis (1 subject), pericarditis (1 subject), and mitral

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	VCG									
	P loop									
	Rotation			Initial vector			Greatest vector			
Duration (cm./sec.)				Direction (degrees)			Voltage (mv.)	Direction (degrees)		
	P	S	H	F	S	H		F	S	H
10	CW	CCW	CCW	− 55	− 15	+ 60	0 13	− 30	− 45	− 10
8	CW	SM	SM	−100	− 90	−160	0 11	− 90	− 90	+ 90
8	SM	SM	SM	− 70	− 70	+ 55	0 09	− 60	− 90	− 25
7	CW	CCW	CCW	− 90	− 70	+ 25	0 09	+ 75	− 80	− 40
8	CW	CCW	CCW	− 80	− 75	+ 35	0 10	− 60	− 85	0
10	CW	CCW	CCW	− 50	− 85	0	0 16	− 50	− 95	0
11	CW	CW	CW	− 75	−110	− 80	0 24	− 5	−110	− 80
12	CD	CCW	CCW	− 50	− 50	+ 60	0 13	− 50	−110	− 10
8	CW	CCW	CCW	− 60	− 75	+ 20	0 09	− 50	−110	− 10
9	CD	CD	CD	− 60	− 90	+ 5	0 12	− 50	− 90	+ 5
10	CW	SM	SM	− 80	− 75	+ 15	0 07	− 50	−100	0
11	CW	CCW	CCW	− 50	− 55	+ 30	0 13	− 50	− 80	+ 10
9	CD	CD	CD	− 45	− 50	0	0 10	− 50	− 85	0
8	CD	CW	SM	− 85	−120	− 75	0 16	− 75	− 95	− 35
11	CD	CCW	CCW	− 35	− 40	+ 70	0 17	− 45	−105	+ 10
12	CW	CW	CW	−110	− 95	−120	0 40	−105	−105	−100
10	SM	SM	Ind.	−100	− 95	—	0 15	− 90	− 90	—
11	SM	CW	CW	− 50	− 90	0	0 36	− 40	− 30	+ 90
10	CW	CCW	CCW	− 70	− 75	+ 70	0 10	− 35	−150	− 0

CW, clockwise rotation; CCW, counterclockwise rotation; CD, closed morphology of P loop; SM, slight morphology of P loop; In., indeterminate.

groups of right and left atrial activation, always evident in the presence of sinus rhythms, proved impossible.

In spite of the large variability in the VCG characteristics, the vectorial orientation and the rotation in the frontal plane was similar in many cases. Some types of IAR could be differentiated by the behavior of the P loop in the horizontal plane (see Discussion).

Discussion

Before discussing the value of the VCG in the IAR, a critical evaluation of the limits of this investigation seems appropriate.

First, the very high degree of amplification employed to obtain VCG tracings that could be adequately analyzed could cause some distortion. However, the VCG's were selected from among our finest tracings, the recording of which did not show interference in the signal or significant changes in the morphology and vectorial orientation between low and high amplification.

Secondly, the theory of a single origin for all activation vectors, recorded by the ECG or VCG in accordance with dipole theory, is still the subject of strong criticism. Consequently, it doesn't seem justified to infer the exact pattern of atrial activation from the orientation of the VCG loop. However, the correlation is accepted between the sinus P wave or loop and the activation process, at least with reference to the general spatial-chronological relations.[3,4]

Finally, the atrial structural alterations, congenital or acquired, could affect the vectorial orientation in nodal rhythms. In the diseases with anatomic and/or functional alterations of the atria (atrial septal defect, endocardial fibroelastosis, mitral stenosis) no correlations were observed

Table I Electrocardiographic and vectorcardiographic data of 18 patients with inferior atrial rhythm

Patient	No	Age (years)	Sex	ECG P R (cm /sec.)	ECG AP (degrees)	ECG I	ECG II	ECG III	ECG a1 L	ECG a1 F	ECG 1	ECG F
R. G	1010	9	M	10	− 50	+	−	−	−	In.	+	+
Z. F	991	8	M	11	− 90	+−	−	−	+	+	−+	−
T A.	1014	10	F	13	− 60	+	−	−	+	+−	+	+
S. E.	936	29	M	Retrograde	− 70	+	−	−	+	+	+	+
S. R.	990	17	F	13	− 60	+	−	−	+	In.	+−	+
Z. W }	1076A	10	M	13	− 50	+	−	−	+	−	In.	+
	1076B			13	− 85	+	−	−	+	+	−	−
Z. F	882	22	M	16	− 75	+	−	−	+	+	+−	+
P M	1013	19	F	10	− 60	+	−	−	+	In.	+−	+
P S.	1048	18	M	13	− 0	+	−	−	+	+	+−	+
P L.	1024	37	F	12	− 60	+	−	−	+	In.	+−	+
C. M	958	22	F	8	− 55	+	−	−	+	+−	+−	+
T A.	1049	9	F	12	− 60	+	−	−	+	In.	+	+
L. A.	932	2	M	9	− 85	+−	−	−	+	+	−+	+
M F	31	8	M	9	− 50	+	−	−	+	In.	+	+
B F	861	9	M	13	−120	−	−	−	−	+	−+	−
C. F	1051	18	M	12	− 90	+−	−	−	+	+	In.	−
C G.	1063	17	M	11	− 60	+	−	−	+	In.	+	+−
C. B	934	9	M	10	− 50	+	−	−	+	+−	+−	+

Abbreviations F frontal S, sagittal; H, horizontal plane P R interval and P loop d ration in centimeters per second Ind., indeterminable P wave; etrograde is related t A V conduction.

and negative in 1 In V_1 it was positive in 14 subjects negative in 4 and diphasic (+−) in 1

In summary the P wave presented the characteristics of *superior nodal rhythm in* 8 cases (31 932 934 958 994 1013 1040 and *1063)* of *inferior nodal rhythm* in 1 case (936) and of coronary sinus rhythm in 10 cases (861 882 990 1024 1044 1048 1049 1051 and 1076 A and B)

VCG findings (*Table I*) The rotation of the P loop in the three planes was constantly abnormal as the normal combination of *counterclockwise rotation in the* frontal and horizontal planes and of clockwise rotation in the right sagittal plane was never observed The counterclockwise rotation in the sagittal and horizontal planes and the clockwise rotation in the frontal plane were predominant. The closed and eight *morphology* were frequently observed The initial limb of the P trajectory (first vector) was oriented between −45 and −110 degrees in the frontal plane (Fig 1 *A*) The greatest vector (highest voltage vector) was oriented between −30 *and* −*105 degrees in the* frontal plane (Fig 1 *B*) and between −30 and −150 degrees in the sagittal plane (Fig 1 *C*) The spatial voltage of the greatest vector varied from 0 07 to 0 40 mv with an average of 0 15 mv and did not show any relationship to the different ECG and VCG types of IAR The duration of the P loop was normal (≤ 0 10 second) in 13 subjects *and slightly increased in 6 however* it never exceeded 0 12 second

In summary the P loop of these ectopic rhythms was markedly modified in all cases. The change affected not only the rotation in the three planes and the direction of the principal vectors but also the general morphology of the loop As a consequence the distinction between the two vectorial

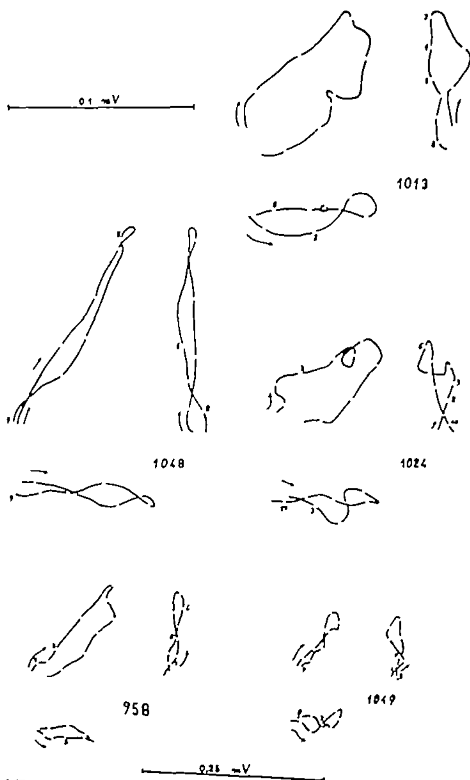


Fig. 3. Five cases of IAR, Type B. Notice in the horizontal plane the elongated-eight morphology of the P loop hich is oriented from right to left with clockwise rotation in the frontal plane.

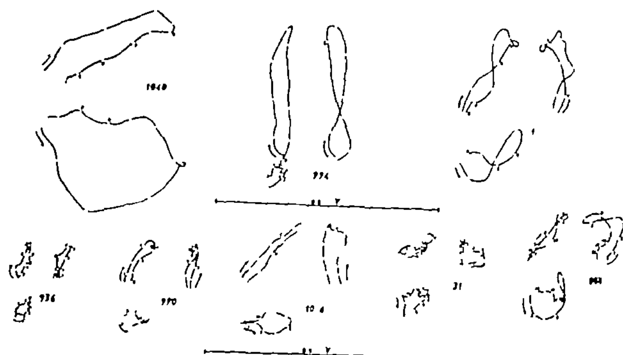


Fig. 2. Eight cases of IAR Type A. *F*, *S*, and *H* are the frontal, right sagittal, and horizontal planes, respectively. The small numbers of the trajectory of the P loop indicate the time in hundredths of a second. Notice the counterclockwise rotation in the horizontal plane, the orientation from right to left (except Case 994) and the clockwise rotation in the frontal plane.

between the VCG patterns and these diseases.

Accepting the hypothesis of the correlation between the atrial ECG or VCG and activation, any abrupt change of the orientation and sequence of the vectors, especially those affecting the first portion of the P wave, must be attributed to an anomalous origin of the pacemaker. Despite the possibility that these changes are related to problems of intra-atrial conduction, we believe this hypothesis to be less likely.* Moreover, the direction of the initial and principal vectors of an ectopic P can suggest the approximate location of the pacemaker, as well as the sequence of all vectors may indicate the pathway followed by the anomalous activation.

In conclusion, the ECG and VCG patterns of our subjects suggest (1) an IAR because of the upward orientation of the principal vectors of the P wave, and (2) activation of the right atrium precedes activation of the left atrium because of the clockwise rotation of the P loop in the frontal plane. The VCG has proved superior to the ECG as both show the upward orientation of ÂP, but only the VCG shows the sequence of the right and left atrial potentials.

The morphology and the vectorial orientation of the P loop in the horizontal plane are particularly interesting and permit the recognition of some principal types of IAR. Type A. The loop has a predominant counterclockwise rotation, with or without eight morphology, and is oriented to the left, and in one subject is oriented to the right and anteriorly (Fig. 2). Type B. The loop is elongated leftward and has an eight morphology (Fig. 3). Type C. The loop has clockwise rotation and is oriented posteriorly (Fig. 4). Rare types. In these subjects the upward orientation affects only a portion of the P loop and the morphology is variable (Fig. 5).

In relation to the ECG classification of nodal and coronary sinus rhythms based on the P-R interval, the VCG has not shown distinct patterns between the two groups. Since the different location of the pacemaker inside the A-V node or from the coronary sinus area could lead to a different sequence of the vectors, we believe the ECG distinction is not acceptable.*

On the contrary, the various VCG types observed in the horizontal plane correspond

*During the preparation of this manuscript, a paper by Waldo and colleagues[18] was published which, from the electrophysiologic point of view, seems to confirm our data exactly.

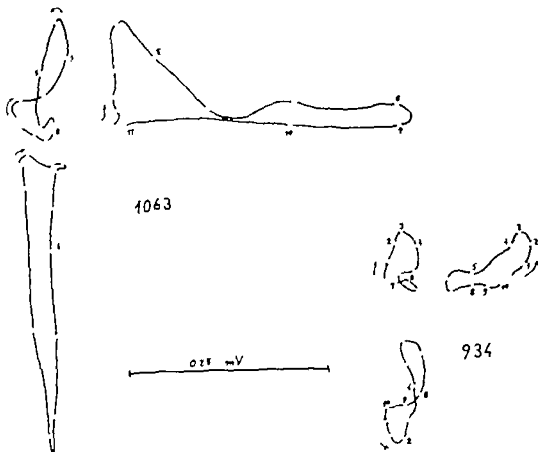


Fig. 5 Two cases of IAR, "rare" type. Notice that only the first portion of the loop is directed upward.

annuli and so forth. Moreover it does not seem possible to distinguish between a true inferior atrial and an infranodal rhythm. Therefore, the distinction between the two types of coronary-sinus and nodal rhythm does not seem adequate, but the possibility of different types of ectopic rhythms must be admitted in accordance with the above mentioned automatic areas.

These automatic areas are scattered on a horizontal plane located at the base of atria. Consequently for any ectopic P wave, originating from one of these points, the horizontal plane will give an orientation and rotation of the loop depending on its (right or left) point of origin the frontal and sagittal planes show principally the upward orientation of the forces.

In summary, both recent electrophysiologic studies[2,1] and this vectorcardiographic analysis permit IAR to be re evaluated as follows (1) The IAR can originate from different points in the right and left atrium. (2) The activation spreads from below upward the potentials directed mainly in this direction can be analyzed in the frontal and sagittal planes of the VCG (3) The horizontal plane gives information about the origin of the pacemaker through the direction and the sequency of the loop. (4) The A V node, probably cannot generate ectopic rhythms. The classical ECG distinction between superior medial and inferior nodal rhythms and coronary sinus rhythm does not appear confirmed either by the electrophysiologic investigations or by the vectorcardiographic patterns. (5) It seems acceptable that both the nodal superior and coronary sinus rhythms originate from one of the inferior atrial areas, where the existence of automatic cells has been documented the medial and inferior

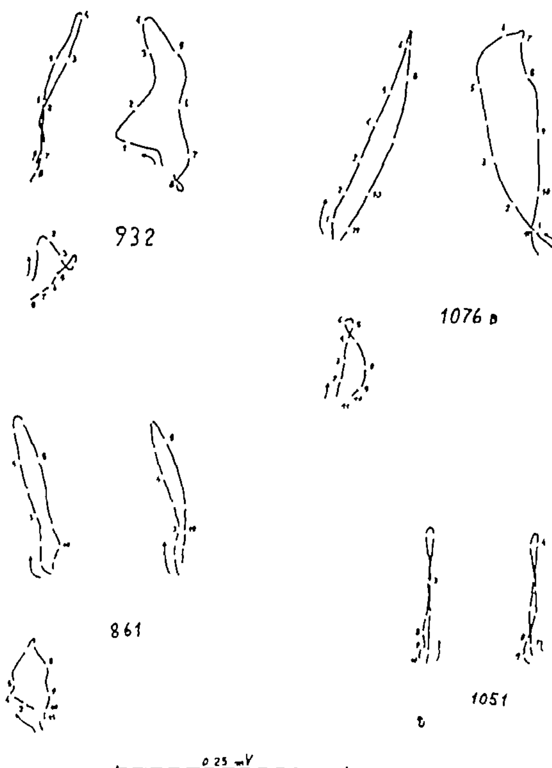


Fig. 4. Three cases of IAR, Type C (Cases 932, 1076B and 861) and one patient with IAR (Case 1051) in whom the P vectors are perpendicular to the horizontal plane. Notice the posterior direction of the horizontal loop in the cases of Type C.

to different ectopic IAR (or infranodal rhythms). This hypothesis is in complete agreement with some recent experimental investigations[9,10] which can lead to some theoretical considerations. Hoffman and Cranefield[3] have not been able to demonstrate the presence of automatic cells in the A-V node, while they are present in the atrial A-V node region between the A-V node and the bundle of His, proximal to the connection of the coronary sinus with the right atrium surrounding the A-V

Irregular recycling of demand pacemakers from borderline electrographic signals

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A demand (ventricular inhibited) pacemaker postpones its next pacing impulse for a preset period known as the escape or recycling interval whenever it detects spontaneous ventricular depolarization. This escape interval is relatively constant for any given demand pacemaker. In most clinical situations the sensing mechanism of demand pacemakers responds to incoming signals in an all-or-none fashion with respect to its recycling property. Thus spontaneous beats recycle the pacemaker with a complete escape interval when they are sensed but do not affect it when they occur within the pacemaker refractory period or if the amplitude of their electrographic signal falls below the threshold required to activate the demand circuit.

During external chest-wall stimulation, however, electric signals which generate only borderline intracardiac voltage for sensing may cause partial suppression, i.e., partial recycling, of certain normally functioning demand pacemakers. In this situation irregular recycling of the pacemaker produces a complex arrhythmia characterized by irregularly shortened escape intervals. This report describes the clinical counterpart of these observations in three patients with normally functioning demand pacemakers that exhibited irregular recycling from borderline spontaneous electrographic signals, a pacemaker response we have designated as partial sensing.

Definition of terms

Pacemaker refractory period. This is the period during which the demand mechanism becomes unresponsive to external or internal electrical stimulation.

DELIVERY REFRACTORY PERIOD. This is the pacemaker refractory period following the emission of a pacing pulse. Its value for Medtronic demand pacemakers Model 5841 is 380 to 440 msec.[3] and for Model 5842 is 160 to 260 msec.[4]

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nodal rhythms take origin below the A V node (6) We propose the old classification of *nodal and coronary sinus rhythms to be* changed to that of IAR in the sense that the atria are activated from below upward It is beyond the limit of this paper to state if the origin is really in the inferior atrial areas or in the infranodal region

Summary

The vectorcardiographic analysis of 19 subjects with inferior atrial rhythm as diagnosed by the ECG has resulted in the following conclusions

1 There is a predominance of clockwise rotation of the *P* loop in the frontal plane and counterclockwise rotation in the horizontal and right sagittal planes

2 The *initial limb of the loop* and the greatest vector are directed upward and usually leftward

3 The spatial voltage of the greatest vector and the loop s dimention are within normal limits.

4 No correlation has been observed between the VCG and the ECG classification of *nodal and coronary sinus rhythms*

5 The analysis of the horizontal plane permits the identification of several types of IAR probably based on a different site of the pacemaker

The suggestion is proposed to change the classification of nodal and coronary sinus rhythms to inferior atrial rhythms

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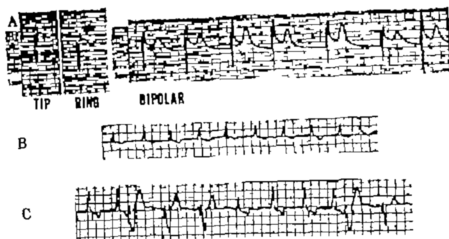


Fig. 2. Tracings from Patient 1. *A*, 1 mv calibration precedes the electrograms. Unipolar recordings from the *tip* and *ring* (proximal) electrodes measure over 7 mv. Note the remarkable similarity of the unipolar electrograms. The *bipolar* electrograms recorded during deep respiration fluctuate in voltage from 3 mv in the last beat to 2 mv in the second from last beat. *B* shows complete suppression of the new 5842 Medtronic demand pacemaker by the accelerated spontaneous rhythm. *C* shows pacing capability of the pacemaker by conversion to fixed-rate mode by application of special magnet. Only stimuli falling outside the refractory period of the heart are effective.

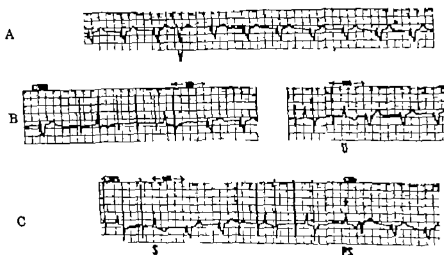


Fig. 3. Tracings from Patient 1 ith Medtronic 5842 demand pacemaker. *A* shows regular ventricular pacing with an E E interval of approximately 880 msec. and sensed ventricular extrasystole (*V*) with an escape interval of 900 msec. (The escape and utomatic intervals are virtually identical in Model 5842.) *B* (left panel) complete suppression of the implanted pacemaker by chest-wall stimulation (black dots). The escape interval following sensed external stimulus measures pproximately 860 msec. The normal QRS (right panel) (*U*) is unsensed by the pacemaker which is completely recycled by the third chest wall stimulus with an escape interval of 860 msec. *C*, chest-wall stimulation. The second QRS (*S*) completely recycles the pacemaker with an escape interval of 860 msec. Since the 1 120 msec. interval from the last chest-wall stimulus (which must have been sensed, since the sensing refractory period of Model 5842 measures less than 125 msec.) to the ensuing demand-pacemaker spike exceeds the escape interval after sensed external stimulus, the QRS complex, (arrow) by generating borderline voltage, partially inhibited the pacemaker and caused partial sensing (*PS*) ith short escape interval of 320 msec.

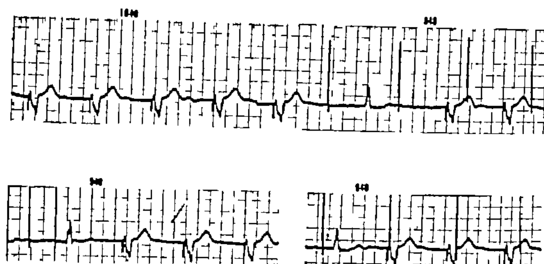


Fig 1 Tracings from Patient 1 with a Medtronic 5841 demand pacemaker The upper panel on the left shows regular ventricular pacing with an E E interval of 1 040 msec. and, on the right suppression of the implanted demand pacemaker by chest wall stimuli (black squares) The pacemaker does not sense the third external stimulus because it falls within its delivery refractory period of 400 msec. On the lower panel chest wall stimulation[1,4] demonstrates sensing of the normal QRS and recycling of the pacemaker with an escape interval of 940 msec. In Model 5841 the escape interval although shorter than the automatic interval remains constant for any particular signal and the escape interval after a sensed chest wall stimulus is shorter than that following a spontaneous beat.[1] Both spontaneous QRS complexes and their preceding external stimuli are sensed by the pacemaker because of it relatively short sensing refractory period. (E E interval is the interval between two consecutive pacemaker pikes during continuou pacing)

SENSING REFRACTORY PERIOD This is the pacemaker refractory period following sensing of a spontaneous beat or intracardiac signal generated by external chest wall stimulation The value for Medtronic demand pacemakers Model 5841 and 5842 is less than 125 msec [3]

Case reports

Patient 1 A demand pacemaker (Medtronic Model 5841) was implanted pervenously in a 78-year-old man for atrial fibrillation with a high degree of atrioventricular block and multifocal ventricular extrasystoles n the presence of congestive heart failure. The bipolar pacing catheter (Medtronic 5818) was positioned at the apex of the right ventricle where the threshold for pacing was about 1 Ma. Ventricular electrograms were not recorded but an electrocardiogram (ECG) showed demand ventricular pacing

The patient became asymptomatic, and several follow up ECG revealed normal function of the pacemaker Sixteen months after pacemaker implantation during apparent fixed-rate pacing the capability of the pacemaker to sense the normal QRS was demonstrated by chest wall stimulation (Fig 1)

Twenty-one months after impla tation the pacemaker was replaced prophylactically by a 5842 Medtronic demand unit. Chest x rays before and after surgery showed no apparent change in the position of the pacing catheter since its original insertion. Unipolar electrograms from the tip and ring (proximal) electrodes measured over 7 mv while long recordings of the bipolar electrogram during quiet and deep respiration registered an effective voltage for sensing, (nadir of S to the apex of R) varyi g from 2 to 3 mv (Fig 2, A) At operation, acceleration of the pontaneous ventricular rate completely suppressed the 5842 demand pacemaker in long recordings during quiet and deep respirations (Fig 2 B) but its pacing ability was tested by conversion to a fixed-rate unit by the application of a special magnet (Fig 2 C).

The day after replacement the ECG recorded regular ventricular pacing occasionally interrupted by sensed ventricular extrasystoles (Fig 3 A) The pacemaker response to the normal QRS was studied by chest wall t mulation which revealed sensed (*S*) unsensed (*U*) and partially sensed (*PS*) beats (Fig 3 *B* and *C*) The ECG was then recorded on magnetic tape for ten hours by the Holter monitoring technique. Analysis of the ten-hour tape revealed sensed unsensed and partially sensed beats and demonstrated that whenever a pacing stimulus fell on the apex of the T wave of a spontaneous beat the generated paced ventricular beat was followed by a spontaneous ventricular extrasystole. Representative recordings from the ten-hour tape in Fig 4 illustrate varying degrees of partial sensing with irregularly shortened escape intervals ranging from 280 to 700 msec. Partial and complete sensing noted in subsequent ECG s were eliminated by conversion to fixed rate pacing with the special magnet.

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Avionics Research Products, Los Angeles, Calif.

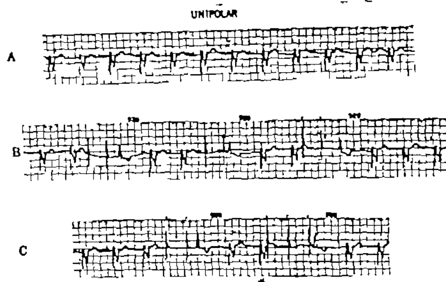


Fig. 5 Tracings from Patient 1 with Medtronic 5842 pacemaker ith a unipolar system. *A* shows apparent fixed-rate ventricular pacing *B* and *C*, chest wall stimulation (depicted by black dots) demonstrates the capability of the pacemaker to sense the normal QRS. The escape interval after QRS sensing measures 920 msec., 60 msec. longer than during bipolar pacing (Fig 3). The slight prolongation of the escape interval appears to result from (1) lteration of the QRS signal causing delayed delivery of threshold voltage to the pacemaker and (2) reversed signal polarity which may reset the sensing circuit, with a delay of 35 msec. for this particular pacemaker

sensing circuit of the pacemaker (Fig 6, *A* and *B*) e failed to appreciate t the time the presence of partial sensing which was subsequently noted in very short ECG recording panel *C*). Chest-wall stimulation readily suppressed the pacemaker out side its delivery refractory period (panel *D*).

Patient 3 A 5842 Medtronic demand pacemaker was impla ted epicardially with bipolar pacing system in 62-year-old man with complete trio-ventricular block, after repeated ttempts at per venous pacing failed to produce consistent ventricular capture. Several postoperative ECG and ten-hour Avionics recording showed normal ventricular pacing Seven weeks after implantation the F E interval (interval between two consecutive pacing stimuli during continuous pacing) became intermittently prolonged to less than twice its basic duration of 840 msec. (Fig. 7 *C* and Fig 8). The delivery refractory period of the pacemaker deter mined by chest wall stimulation was normal t 240 to 260 msec. (Fig 7 *A* and *B*). Simultaneous recording of esophageal and surface ECG established the diagnosis of T-wave sensing (Fig. 7 *C*) Slight prolongation of the fourth E E intervals in Fig. 8, *C* nd *E*, by only 120 and 140 msec., respectively indicates that the pacemaker was partially recycled from a borderline signal originating from the T wave of the fourth beat (see legend for explanation) Conversion to fixed-rate pacing with the special magnet produced absol tely regular ventricular pacing. The demand pacemaker was replaced by fixed-rate type to avoid the hazard of bradycardia from continuous T-wave sensing after long ecordings of the ventricular electrograms from each epicardial electrode failed to suggest the diagnosis of wire fracture. The patient has remained well with normal fixed-rate pacing for several months, at the time of his last follow-up. The removed demand pacemaker was examined by the manufacturers, who found no evidence of malfunction.

Discussion

We have evaluated the performance of implanted Medtronic (Models 5841 and 5842) and American Optical demand pacemakers by chest wall stimulation and observed an all-or-none response to incoming signals with response to behavior of the escape interval except when the external stimuli generate intracardiac voltage of threshold amplitude for sensing[1,4] (Fig 9) When one of these pacemakers senses an adequate signal the output stages of its amplifier become completely saturated thereby completely discharging the timing capacitor that regulates th firing rate of the pacemaker However borderline signals within a small range of signal strength induce incomplete saturation of the output stages of the amplifier and cause premature delivery of the next pacemaker impulse because of incomplete discharge of the timing capacitor[7] This causes irregular recycling

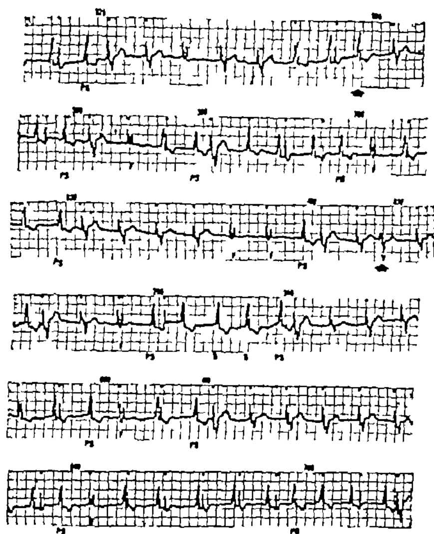


Fig. 4. Tracings from Patient 1. Representative panels from a ten hour Avionics recording after implantation of 5842 Medtronic demand pacemaker. Stimuli from the implanted pacemaker are depicted by black dots. The duration of the escape intervals in milliseconds following sensed and partially sensed beats are shown above the ECG's. Because the speed of the Avionics recording is slightly faster than the standard ECG, all intervals are slightly shortened so that the basic E-E interval measures only 800 to 840 msec. The tracings show normally paced beats, true fusion beats[1] (*F*), unsensed (*U*), sensed (*S*), and partially sensed (*PS*) beats. In the upper panel the arrow points to a normally sensed QRS that completely recycles the pacemaker with an escape interval of 800 msec. In the third panel the arrow points to a sensed ventricular extrasystole (*V*) which also completely recycles the pacemaker with an escape interval of 840 msec. Whenever partial sensing occurs, the E-E interval becomes prolonged, and incomplete recycling of the pacemaker leads to considerable variation of the escape interval from 260 to 700 msec.

Because the Avionics recording suggested the potential risk of a repetitive ventricular response from pacemaker stimuli occurring on the apex of the T wave, the normal demand response of the pacemaker was restored by utilizing the larger unipolar voltage for sensing. The threshold for unipolar ventricular pacing was determined with the indifferent (anode) electrode in the pacemaker pocket. Since the threshold for pacing measured with a 2 msec. pulse was 10 Ma. when the tip was the cathode but fell to 5 Ma. when the proximal (ring) electrode became the cathode, the bipolar system was converted to a unipolar system with the proximal electrode as the cathode. Subsequent ECG's showed apparent fixed-rate pacing but chest wall stimulation repeatedly demonstrated normal QRS sensing with an escape interval of 920 msec. (Fig. 5) 60 msec. longer than the escape interval during bipolar sensing (Fig. 3). This pacemaker was still functioning normally five months after its conversion to a unipolar system. Several follow-up measurements of the automatic interval with an electronic counter were constant, and the escape interval and delivery refractory period also remained unchanged.

Patient 2. This patient with a 5841 Medtronic demand pacemaker was previously described to illustrate undersensing of the QRS complex due to a low voltage bipolar electrogram, despite the presence of much larger unipolar voltage from the tip and ring electrodes. Though the bipolar voltage fell intermittently below threshold level to activate the

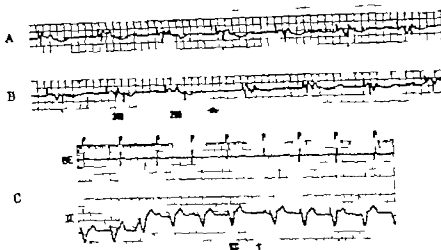


Fig. 7 Tracings f om Patient 3. *A* nd *B* (50 mm. per second recording speed) show determination of the delivery refractory period of Model 5842 pacemaker by chest-wall timulation. Stimuli from the implanted pacemaker are above the isoelectric line while the chest-wall stimuli, depicted by black dots, fall below the isoelectric line. The E E interval measures 840 msec. The pacemaker senses only the third chest wall stimulus in *B* 260 msec. after firing, and completely recycles itself with an escape interval of 840 msec. (arrow). Since the second chest-wall stimulus in *B* is unsensed 240 msec. after pacemaker discharge, the delivery refractory period measures 240 to 260 msec. *C*, simultaneous recording of filtered bipolar esophageal Lead[4] (*BE*) and Lead II of the ECG. The basic E-E interval is 840 msec. Oversensing causes prolongation of the sixth E-E interval t 1,200 msec. The fifth P wave (within the sixth QRS complex) falls in the delivery refractory period of the pacemaker and therefore cannot be sensed. If oversensing had not occurred the pacemaker would have fired t the point marked by the arrow 160 msec. before the onset of the sixth P wave. This excludes partial recycling of the pacemaker from a borderline signal originating from the sixth P wave. Therefore, the abnormal recycling of the pacemaker ppears t be due to sensing of the relatively high voltage generated by the T wave of the sixth paced beat.

rate of the pacemaker Differential diagnosis of T-wave sensing of paced ventricular beats also includes sensing of the returning voltage to the pacemaker after the emission of a pacing pulse (nonsymetrical wave form) This time-changing voltage may be sensed if it generates a sufficiently strong signal despite the low frequency rejection circuit when the pacemaker regains its sensing capabil ty at the end of the refractory period. Such a mechanism would lead to oversensing with an E E interval equivalent to the sum of the refractory period and one escape interval This possibility may be excluded in Patient 3 because in Fig 8 *A* the second prolonged E E nterval measures 1,290 msec. a value exceeding by 200 msec. the sum of 840 msec. (escape interval) and 250 msec. (delivery refractory period) Intermittent derangement of the pacing circuit may occur with a fractured wire when intermittent apposition of the fractured ends produces a particular form of oversensing resembling sensing of the T wave paced beats.[8,1] However this mechanism was excluded in Patient 3 because no loose connections were found at operation and a wire fracture was ruled out by recording normal ventricular electrograms from each epicardial electrode and because the patient has demonstrated regular pacing for several months with the same electrodes in situ

Though the voltage of the bipolar electrogram in Patient 1 was adequate to suppress the 5841 Medtronic demand pacemaker with an input sensitivity of 0.8 to 1.4 mv., it could not completely inhibit Model 5842 with a lower sensitivity of 1.5 to 2.5 mv Since bipolar electrograms were not recorded at the time of the original implantation no definite conclusions may be drawn but three factors could diminish the amplitude of a bipolar signal with the passage of time (1) changes in morphology and size of unipolar electrograms from a local reaction under the electrodes[11] (2)

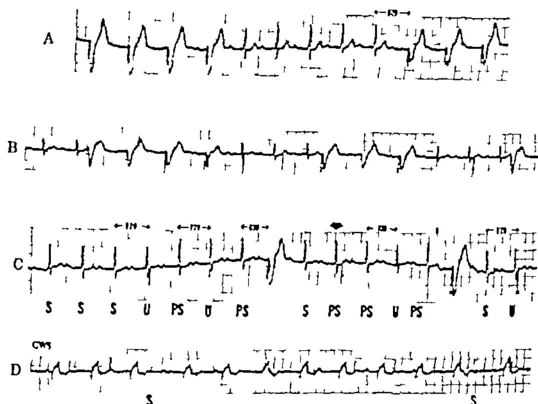


Fig. 6. Tracings from Patient 2 with a Medtronic 5841 pacemaker. *A* shows normal ventricular pacing and QRS sensing. The fifth QRS complex completely recycles the pacemaker with an escape interval of 820 msec., which for this particular model is normally shorter than the E-E interval of 900 msec. *B* shows fixed-rate pacing with all spontaneous beats unsensed by the pacemaker. *C* shows sensed beats (*S*), unsensed beats (*U*), and partially sensed beats (*PS*). Stimuli from the implanted pacemaker are depicted by black squares. The duration of the escape intervals in milliseconds following sensed and partially sensed beats is shown above the ECG. The first and last escape intervals are normal for this particular pacemaker. All other escape intervals are irregularly shortened from 610 to 720 msec. The interval from the onset of the fourth sensed QRS to the subsequent pacemaker stimulus measures about 900 msec., 80 msec. more than the normal escape interval. Therefore, the QRS complex labeled by the arrow is in all probability partially sensed and recycles the pacemaker with a very short escape interval of about 160 msec. *D*, chest wall stimulation (*CWS*) is depicted by the black dots. Only external stimuli (*S*) falling outside the 440 msec. delivery refractory period of the pacemaker completely recycle the pacemaker with an escape interval of 760 msec., 140 msec. shorter than the E-E interval, but a normal response for Model 5841.

of the pacemaker and is represented electrocardiographically by irregularly shortened escape intervals[8] creating a complex arrhythmia we have called partial sensing.[1] In contrast, our experience with a few external demand pacemakers (Medtronic 5840 and 5880) suggests that their demand mechanism behaves in an all-or-none fashion.

Electrographic signals of threshold amplitude capable of causing partial sensing may be generated by: (1) low voltage bipolar electrograms of normal beats (Patients 1 and 2) or ventricular extrasystoles, (2) low voltage electrograms when a pacing catheter perforates the heart,[8] (3) unusually sharp rising T waves of high voltage (Patient 3), and (4) high-amplitude P waves.

The diagnosis of partial sensing by demand pacemakers may be easily confirmed by conversion to fixed-rate pacing which eliminates all arrhythmias specifically related to the sensing mechanism. Inspection of the prolonged E-E intervals in Fig. 8 *A* and *B* illustrates how complete or near complete sensing of a high voltage T wave may mimic partial P wave sensing. The distinction is important because T wave sensing only causes pacemaker bradycardia while P wave sensing, if it becomes complete, carries the hazard of precipitating ventricular asystole or severe bradycardia when the sinus rate exceeds the automatic

with respect to its recycling property However electrographic signals of threshold amplitude for sensing may cause partial suppression (irregular recycling) of certain normally functioning demand pacemakers and produce a complex arrhythmia designated as partial sensing and characterized by irregularly shortened escape intervals. Partial sensing disappears by conversion to fixed-rate pacing thereby eliminating all arrhythmias specifically related to the sensing circuit. This report describes partial sensing by normally functioning demand pacemakers from borderline signals due to low bipolar ventricular electrograms in two patients and originating from the T wave in the third patient The recognition that this particular arrhythmia stems from the delivery of an inadequate signal to a pacemaker rather than true pacemaker failure may avoid unnecessary replacement of normally functioning pulse generators.

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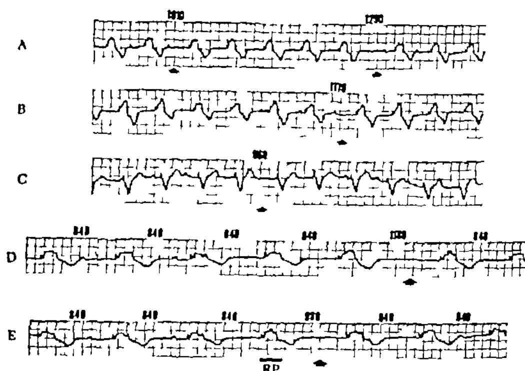


Fig. 8. Representative tracings from patient 3 showing sensing of the T wave by the 5842 Medtronic demand pacemaker. The duration of the E-F interval in milliseconds is shown above the ECG's. *D* and *E* were recorded at the speed of 50 mm. per second. The normal E-F interval is 840 msec. except where marked by the arrows where it lengthens from 960 to 1,290 msec. because a relatively high voltage signal from the T wave of preceding beat completely or incompletely recycles the pacemaker. When the T wave completely recycles the pacemaker the minimum F-E interval cannot be shorter than 1,090 msec. which is the sum of a normal escape interval of 840 msec. or more and the delivery refractory period of 250 msec. (escape interval of Model 5842 virtually equals the automatic interval). Therefore, the F-F interval of 1,290 msec. in all likelihood represents complete recycling of the pacemaker from sensing the tail end of the T wave of the preceding beat. However, in *E* the fourth E-F interval is only prolonged to 980 msec. Since the earliest possible time that the T wave can be sensed is 250 msec. after pacemaker discharge, the recycling time prior to firing of the fifth beat cannot exceed 730 msec. This abnormally short recycling with an escape interval of 730 msec. or less is consistent with partial sensing of a borderline T wave signal.

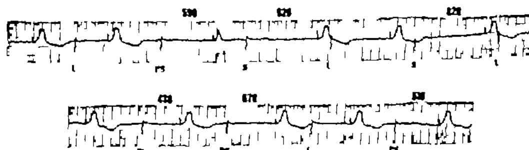


Fig. 9. Effect of external chest wall stimulation of threshold amplitude on an American Optical demand pacemaker. The delivery refractory period determined by chest wall stimulation measured 140 msec. The escape interval after complete sensing of an external stimulus (*S*) measures 820 msec. Some stimuli induce partial sensing (*PS*) with irregularly shortened escape intervals varying from 430 to 590 msec. When the amplitude of the external stimuli was increased, all the stimuli outside the delivery refractory period initiated an escape interval of 820 msec. *U*, unsensed stimuli; *F*, fusion beat. (Recording speed was 50 mm. per second.)

movement of the bipolar pacing catheter even if undetectable radiologically may produce a profound change in the bipolar electrogram,[4] and (3) altered activation of the heart, as in myocardial infarction.

Summary

In most clinical situations the sensing mechanism of demand (ventricular inhibited) pacemakers responds to incoming signals in an all-or-none fashion

Table I. A review of previous recommendations for bed rest in acute myocardial infarction

Reference	*Year*	*Recommendation for bed rest*
Lewis[1]	1937	8 weeks bed rest
Levine[2]	1940	4-8 weeks in bed
Levine[3]	1951	4-8 weeks at rest
Levine and Lown[4]	1952	63 of 73 patients in chair by third day
White[5]	1945	1 month bed rest
Irvin and Burgess[6]	1950	2 week in bed
Brummer, Linko, and Kasanen	1956	16 days bed rest
Brummer, Linko, and Kallio[8]	1961	12 days bed rest
Wood[9]	1960	3-6 weeks in bed
Wood	1968	2 weeks in bed
Friedberg[11]	1966	2-3 weeks minimum bed rest
Lauper, Lichtlen, and Rossier[12]	1966	Armchair treatment beginning second week
Lal and Caroll[13]	1968	Ninth day in chair
Naughton et al.[14]	1969	Up for meals third day; up every 2 hours on fifth day

Table II. Summary of the population in the present study regarding total admissions, deaths, sex ratio, and readmissions

	First admission	*Second admission*	*Third admission*	*Total*
Deaths				
Men	24	4	2	30 (56.1)
Women	8	0	0	8 (53.6)
Total	32	4	2	38
Live discharges				
Men	199 (51.0)	21	1	221 (51.5)
Women	50 (55.6)	4	0	54 (55.9)
Total	249 (52.0)	25 (56.0)	1	275 (53.8)

Mean age in years is given in parentheses.

gether they cared for 235 (85.5 per cent) of the patients in this study. Patients of physicians in practice as associates were grouped together. The remaining 10 physicians, each of whom treated less than 10 patients, were classified under "other physicians" and their data for 40 patients were pooled.

Results

The sex distribution, deaths, and readmissions during this four year study are outlined in Table II.

There were 38 deaths while the patients were hospitalized. Twenty patients died on the first hospital day, 1 on the third, 3 on the fourth, 2 between the fifth and seventh, 8 between the eighth and fourteenth, 2 between the fourteenth and twenty-first, and 2 after the third week. Thirty-three of the above patients had never been allowed out of bed. The remaining 5 patients died on Days 8, 11, 13, 15, and 24, having been permitted out of bed for the first time on Days 7, 9, 11, 3, and 2, respectively. Four were men, 1 was a woman. Four had a history of previous infarction, and all had enzyme elevations. Three had complications of failure, shock, or cardiac arrest, and 4 had experienced arrhythmias. In 4 the ECG showed an anterior infarction, in 1 a posterior infarction. Autopsy examination

Bed rest in acute myocardial infarction

A study of physician practices

Martin Duke, M.D.
Manchester, Conn.

Criteria for determining the duration of bed rest and of hospitalization in patients with acute myocardial infarction are not clear. Although a liberal trend has developed toward shortening these periods (Table I), a wide diversity of opinion still exists. This study will examine present day practices of physicians in a community hospital regarding the duration of bed rest for patients with acute myocardial infarction.

Methods

The records of all patients 65 years old and younger with a discharge diagnosis of acute myocardial infarction during the years 1965 to 1968 were studied. In order to avoid complicating and associated disabilities of increasing age, patients above 65 years were excluded.

The diagnosis of acute myocardial infarction was made in 313 cases. The following data were extracted from each record: (1) age, (2) sex, (3) duration of hospitalization, (4) duration of bed rest before being permitted into a chair for the first time, (5) the name and age of the attending physician, (6) electrocardiographic diagnosis, (7) arrhythmias permanently recorded either from a monitor or electrocardiogram (ECG), (8) history of previous myocardial infarction, (9) complications such as shock, failure, emboli, and cardiac arrest, (10) enzyme changes including serum glutamic oxalacetic transaminase (SGOT), lactic dehydrogenase (LDH), hydroxybutyrate dehydrogenase (HBD), and creatinine phosphokinase (CPK).

The data was kept as simple and objective as possible. The ECG patterns were classified as anterior, posterior, lateral, S-T T changes (subendocardial or intramural), and others such as left bundle branch block, Wolff-Parkinson-White syndrome, normal, and so forth in accord with standard criteria. Complications were noted as having occurred or not. Enzyme studies were recorded as normal or elevated with no attempt made to evaluate the frequency of the tests. The normal values for the serum enzymes were SGOT 15 to 50 Karmen units, LDH 13 to 120 Wacker units, CPK 0 to 20 Sigma units, and HBD up to 125 Sigma units. An arrhythmia was recorded as either present or not, regardless of type or whether potentially benign or serious; the finding of even one or two premature beats was considered an arrhythmia for purposes of this study.

The data were assembled individually for 11 physicians or groups of physicians, each of whom treated 10 or more patients to-

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...sicians and physician groups

...rrhythmias	Previous infarct	Elevated enzymes	ECG: Anterior	ECG: Posterior	ECG: S-T T	ECG: Lateral	ECG: Others
24 (32)	16 (35)	38 (84)	8 (17)	14 (30)	20 (43)	3 (7)	1
9 (47)	5 (26)	9 (47)	4 (21)	7 (37)	7 (37)	1 (5)	—
6 (40)	6 (40)	12 (80)	3 (20)	3 (20)	8 (53)	—	1
3 (27)	3 (27)	7 (64)	2 (18)	4 (36)	5 (45)	—	—
6 (40)	6 (40)	15 (100)	5 (33)	4 (27)	5 (33)	1	—
5 (33)	2 (13)	13 (87)	7 (47)	6 (40)	2 (13)	—	—
10 (30)	8 (27)	29 (97)	9 (30)	10 (33)	9 (30)	2	—
5 (50)	5 (50)	9 (90)	3 (30)	2 (20)	5 (50)	—	—
7 (50)	7 (50)	13 (93)	—	5 (36)	5 (36)	2	2
13 (39)	5 (15)	24 (73)	9 (27)	10 (30)	12 (36)	1	1
8 (30)	6 (22)	20 (74)	7 (26)	10 (37)	7 (26)	2	1
15 (38)	10 (25)	34 (85)	10 (25)	8 (20)	17 (43)	4 (10)	1
110 (40.0)	81 (29.4)	223 (81.1)	67 (24)	83 (30)	102 (37)	16 (6)	7 (3)

the 275 patients was 24.6 days (men 24.4 days, women 24.8 days). The mean number of days at bed rest before the patients were permitted in a chair was 10.5 days (men 10.5 days, women 10.1 days). Thus patients were kept in bed an average of 43 per cent of their hospital stay.

The mean duration of bed rest ordered by each physician for his patients ranged widely from 7.4 to 15.2 days, with a statistically significant difference observed among many groups (Table III). No recognizable variation in patient population accounted for this, the patients of each physician being of comparable age and having similar patterns of complications, enzyme changes, arrhythmias, previous infarctions, and types of ECG diagnosis (Table III). The

Table III Summary of data from 275 patients with acute myocardial infarction arranged by

Physician age (yr)	*Number of patients and mean age*	*Days of bed rest*	*Hospital days**	*Bed rest / Hospital days* × 100%	*Complications*
A 35	46 53 6	7 4 ±3 6	24 5 ±6 6	30	7 (15)†
B 53	19 52 1	8 1 ±4 5	24 0 ±4 1	32	1 (5)
C 48	15 53 0	8 1 ±3 4	21 6 ±3 1	37	3 (20)
D 36	11 55 3	8 9 ±4 7	28 5 ±6 3	31	1 (9)
E 53 29	15 53 1	9 8 ±4 2	23 2 ±5 5	42	3 (20)
F 46 38	15 52 9	9 9 ±4 5	23 5 ±4 0	42	2 (13)
G 58 38	30 54 4	10 5 ±3 1	20 6 ±5 3	40	6 (20)
H 58	10 57 3	12 3 ±5 8	21 9 ±9 1	56	2 (20)
I 42	14 54 4	13 6 ±5 0	26 6 ±6 4	51	2 (14)
J 46 41 33	33 53 0	14 8 ±5 2	22 9 ±4 3	65	4 (12)
K 42 51	27 50 6	15 2 ±4 6	28 6 ±7 4	53	6 (22)
Group of 10 physicians	40 55 0	9 5	27 1	35	8 (20)
Total	275 53 7	10 5 ±5 1	24 6 ±6 3	43	45 (16 4)

Statistical significance of difference between the mean days of bed rest ordered by physicians
$p < 0.001$ A K, A J A L, A-G B-J B-K, C K, C J E K, D-K, G-K, G-J;
$p < 0.01$ A-H B-I, D-J E-J F K, F J C I;
$p < 0.05$ A-F A-E, B-H, D-I E I C-G, C H G-L
*Mean value and standard deviation.
†Per cent of patients given in parentheses.

in 4 confirmed extensive coronary arteriosclerosis and myocardial infarction without cardiac rupture

The remaining 249 patients combined had 275 episodes of acute myocardial infarction and were all discharged alive from the hospital Since there were no significant differences in age or sex distribution between the patients in the first admission group (249) and those readmitted during the four years of this study (26) the data for the two groups were combined (Table II) There was a 4 1 male to female ratio Both sexes showed a similar proportion of complications arrhythmias prior infarctions serum enzyme changes and types of ECG abnormalities.

The mean duration of hospitalization for

an attempt to show that many patients still appear to be kept in bed and probably in the hospital for excessive and arbitrary periods of time that are not dictated by known facts about the course of this disease.

Summary

Physician practices in prescribing bed rest for hospitalized patients with an acute myocardial infarction were studied The mean duration of bed rest for the patients of each of eleven physicians varied widely and significantly from 7 4 to 13.2 days. No differences in patient population or in the ages or types of practices of the physi cians were found to account for this. Each physician appeared to have a relatively fixed program of bed rest for his patients.

In view of well-established experiences advocating early mobilization in patients with an acute myocardial infarction it was apparent that some physicians are still traditionally bound to prescribing prolonged bed rest. The medical as well as the socioeconomic implications of this are discussed

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Discussion

No objective data could be found to explain why periods of bed rest prescribed by physicians varied widely and significantly from 30 to 65 per cent of the total hospitalization period No differences in patient population could be found The total period of hospitalization was not related to the duration of bed rest The ages of physicians as a reflection of year of graduation showed no pattern to indicate that older or recent graduates were more or less conservative (Table III) General practitioners internists and cardiologists were present at both ends of the spectrum For the most part patients with S-T T changes were permitted into a chair sooner than others this being the practice of ten of the eleven physician groups studied However even here the duration of bed rest still varied widely from physician to physician with a range of 5 to 13 3 days. Although psychological characteristics and the severity and duration of pain surely were important considerations these factors could not be evaluated in a retrospective study of this type

Studies have shown that allowing patients with myocardial infarction out of bed early in the convalescence does not increase the immediate mortality rate or the incidence of cardiac aneurysm myocardial rupture congestive failure or recurrent infarction [4,7,8,9,17] In spite of this many patients are still subjected to a traditional period of prolonged bed rest the disadvantages of which are either not considered or are viewed as more acceptable The benefits of early chair and ambulatory treatment in avoiding thromboembolism [18] in preventing cardiovascular deconditioning [18] and in relieving anxiety [19] together with the absence of complications described above would appear to outweigh concerns of the physician that for the most part seem unfounded

The wide range in length of time of bed rest prescribed would indicate that in some patients objective evaluation played either no role or only a minor one in deciding this phase of treatment If this is so aside from the medical disadvantages previously mentioned an unnecessary socioeconomic burden is being placed upon patients and hospitals. The excessive use of needed hospital beds the increased costs to the patient and the possible prolongation of convalescence and time away from work are all sequelae of what, at times, would appear to be an arbitrary decision regarding the duration of bed rest

Lown and Sidel[20] have stated that patients who are without complications of an infarction during the initial week of hospitalization derive no special benefit by remaining in the hospital beyond the tenth to twelfth day Adgey[21] has shown that in patients hospitalized for an average of 13 1 days there was no apparent morbidity in the two week period after discharge which might have been prevented by a longer hospital stay Similarly Prineas and Lovell[22] demonstrated that a decrease in the average hospital stay from over 4 weeks to 3 weeks or less was not accompanied by an increased mortality during the first 3 months after discharge This is not to imply that the duration of bed rest and hospitalization are to be dictated by a standardized modality of treatment Earlier mobilization has been recommended for a minor acute illness with longer bed rest for those with recurrent chest pain a persistent third heart sound cardiomegaly pulmonary edema or a pronounced precordial pulsation [23]

Unfortunately the ritual of uniformly prescribing prolonged bed rest in all patients with an acute myocardial infarction has become deeply engrained in the minds of many physicians and patients even 19 years after Levine and Lown's initial recommendations.[4] However as stated by Irvin and Burgess [6] It is to be hoped that the treatment of myocardial infarction may one day rest on the results of purposeful clinical study rather than on mere reasoned opinion To this end, the present study is

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Experimental and laboratory reports

Effect of beta adrenergic receptor stimulation on regional myocardial metabolism Importance of coronary vessel patency

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Vassil V Tchokoev MD
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It has been demonstrated in the open chest dog that when total left coronary flow is lowered experimentally the reduction in myocardial tissue flow in the left ventricle is greater in the subendocardium than the subepicardium [1-3] Biochemical signs of ischemia consisting of lactate accumulation and high-energy phosphate bond depletion also are more pronounced in subendocardial tissue [4] Possible reasons for this include (1) greater impairment of blood flow to the deep myocardium because of a transmural gradient in myocardial tissue pressure during systole [5] and (2) higher energy requirements in the deep myocardium due to a transmural gradient in wall stress [6]

The observation that nonuniform changes in myocardial blood flow and metabolism result from a forced reduction in coronary flow suggests that similar changes might result from a forced elevation in contractile activity of the ventricular wall Indeed it has been postulated by others[7] that during cardiac stress the normal left ventricle would exhibit subendocardial hypoxia and anaerobic glycolysis. Such a postulate would appear to have even greater validity in the case of the heart which because of reduced coronary vessel patency was limited in its ability to increase coronary flow There is clinical evidence to support this [8] Further studies on regional metabolism of the stressed heart are indicated to test these hypotheses.

In the present study the open chest dog heart was stressed by the intravenous administration of a beta-adrenergic receptor agonist isoproterenol and a transmural tissue specimen was procured from beating left ventricle for estimating the outer and inner wall levels of pyruvate lactate and tissue water content In order to investigate the effects of reduced coronary vessel patency in some animals the main left coronary artery was cannulated and the tubing of the cannula circuit was partially constricted prior to beta stimulation Control studies were performed on both normal and coronary constricted animals not undergoing beta stimulation

Methods

Experiments were performed on 34 mongrel dogs weighing from 16 to 29 kilograms and fasted for 24 hours. The animals were presedated with morphine sulfate 1 5 mg

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per kilogram and anesthetized with a solution containing chloralose (25 mg per kilogram) urethane (240 mg per kilogram) allobarbital (50 mg per kilogram) and monoethylurea (240 mg per kilogram) Additional amounts were administered as required to maintain prolonged anesthesia. The trunk and limbs of the animal were enclosed in a polyethylene bag to conserve body heat and skin incisions were made through the wall of the bag Rectal temperature recorded with an electric thermometer was maintained between 35 and 37° C. by this maneuver Following endotracheal intubation and mechanical ventilation with room air a left thoracotomy was performed An electromagnetic flow transducer (Biotronex Series 5000) was placed on the aorta just distal to the left subclavian artery for measurement of aortic blood flow with a Biotronex BL-610 flow meter Polyethylene catheters were introduced into the thoracic aorta via a femoral artery the inferior vena cava via a femoral vein and the left ventricle via the left atrial appendage. In some experiments a catheter was also manipulated into the coronary sinus after being introduced into the right jugular vein For coronary constriction studies only cannulation of the main left coronary artery was performed with a self perfusing stainless steel cannula, introduced into the left subclavian artery (Fig 1) When the tip of the cannula was secured in the main left coronary artery segment by an externally placed tie, blood from the root of the aorta entered a side hole in the double-lumen shaft of the cannula, passed up a loop and then returned via the other lumen to the coronary artery The loop contained a section of rubber tubing side taps, and a cannulating type electromagnetic flow transducer (Biotronex, Series 2000) A zero flow signal was obtained by momentarily occluding the rubber tubing Coronary constriction was accomplished by tightening an adjustable snare around the rubber tubing a desired amount. Pressure beyond the constriction site in the coronary circuit was measured with a Statham strain gauge (P23Db) attached directly to the side tap on the cannula loop Pressure in the aortic and left ventricular catheters was measured simultaneously

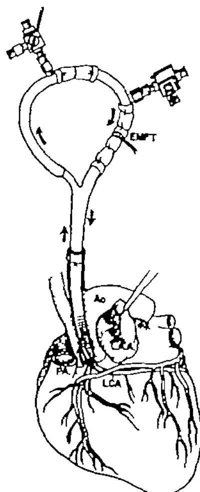


Fig. 1 Diagram of coronary cannula showing its position in the aorta and main left coronary artery Arrows indicate the direction of blood flow through the double lumen shaft of the loop. *A* Aorta, *EMFT* cannulating-type electromagnetic flow transducer *PA* pulmonary artery *LAA* left atrial appendage *LCA* left coronary artery (Reprinted with permission from Gelgas, D M J and associates Medical Research Engineering, 7.30, 1968.)

with additional strain gauges. All signals were inscribed on photosensitive paper using a multichannel oscillograph (Electronics for Medicine Model DR-8) Signals were also recorded on a multichannel tape recorder (Hewlett Packard Model 3907B) for later reproduction at gains and chart speeds best suited for data analysis. Anticoagulation was produced with a single dose of heparin 7.0 mg per kilogram given prior to insertion of catheters or the coronary cannula.

Experimental and laboratory reports

Effect of beta-adrenergic receptor stimulation on regional myocardial metabolism: Importance of coronary vessel patency

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It has been demonstrated in the open chest dog that when total left coronary flow is lowered experimentally, the reduction in myocardial tissue flow in the left ventricle is greater in the subendocardium than the subepicardium.[1-3] Biochemical signs of ischemia, consisting of lactate accumulation and high-energy phosphate bond depletion, also are more pronounced in subendocardial tissue.[4] Possible reasons for this include (1) greater impairment of blood flow to the deep myocardium because of a transmural gradient in myocardial tissue pressure during systole[5] and (2) higher energy requirements in the deep myocardium due to a transmural gradient in wall stress.[6]

The observation that nonuniform changes in myocardial blood flow and metabolism result from a forced reduction in coronary flow suggests that similar changes might result from a forced elevation in contractile activity of the ventricular wall. Indeed, it has been postulated by others[7] that during cardiac stress the normal left ventricle would exhibit subendocardial hypoxia and anaerobic glycolysis. Such a postulate would appear to have even greater validity in the case of the heart which, because of reduced coronary vessel patency, was limited in its ability to increase coronary flow. There is clinical evidence to support this.[8] Further studies on regional metabolism of the stressed heart are indicated to test these hypotheses.

In the present study, the open chest dog heart was stressed by the intravenous administration of a beta adrenergic receptor agonist, isoproterenol, and a transmural tissue specimen was procured from beating left ventricle for estimating the outer and inner wall levels of pyruvate, lactate, and tissue water content. In order to investigate the effects of reduced coronary vessel patency, in some animals the main left coronary artery was cannulated and the tubing of the cannula circuit was partially constricted prior to beta stimulation. Control studies were performed on both normal and coronary constricted animals not undergoing beta stimulation.

Methods

Experiments were performed on 34 mongrel dogs weighing from 16 to 29 kilograms and fasted for 24 hours. The animals were presedated with morphine sulfate, 1.5 mg

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Table I Arterial blood and tissue data obtained on normal animals (mean values and S.E.M for 10 control and 10 beta stimulated animals)

Group	Arterial blood						
	Hct. (%)	P_{O_2} (mm. Hg)	P_{CO_2} (mm. Hg)	pH (units)	Pyruvate (mM)	Lactate (mM)	Lactate/pyruvate (mM)
Control	45 ± 2	84 ± 6	37 ± 1	7.39 ± 0.02	0.106 ± 0.019	0.819 ± 0.160	6.48 ± 0.73
Beta-stimulated	42 ± 2	86 ± 7	32 ± 3	7.40 ± 0.02			
Before					0.103 ± 0.014	0.688 ± 0.176	6.26 ± 1.14
During					0.114 ± 0.014	0.636 ± 0.163	5.61 ± 1.16

Group	Outer and inner ventricular wall			
	Pyruvate (μmoles/Gm.)	Lactate (μmoles/Gm.)	Lactate/pyruvate (μmoles/Gm.)	Tissue H_2O (%)
Control				
Outer	0.111 ± 0.021	0.978 ± 0.157	9.83 ± 1.04	77.4 ± 0.4
Inner	0.124 ± 0.012	1.069 ± 0.134	9.28 ± 0.80	77.9 ± 0.3
Beta-stimulated				
Outer	0.197 ± 0.026 (0.02)*	1.450 ± 0.267	7.73 ± 1.40	77.5 ± 0.4
Inner	0.241 ± 0.040 (0.02) (0.05)†	1.576 ± 0.246 (0.05)†	7.11 ± 1.12	77.9 ± 0.6

*P value for difference between same regions in control group and beta-stimulated group.
†P value for difference between outer and inner wall in beta-stimulated group.

Results

Normal animals Data were obtained on ten noncannulated animals in which beta adrenergic receptor stimulation was achieved by infusing isoproterenol intravenously at a rate of 10 μg per minute for 4 minutes before obtaining a transmural myocardial tissue specimen. Fig 2 is a plot of the measured hemodynamic variables before and during beta stimulation The values obtained before beta stimulation are not significantly different from those obtained in another group of ten noncannulated animals which underwent tissue sampling without beta stimulation. As can be seen from this figure there were substantial increases in heart rate and aortic blood flow accompanied by a modest drop in aortic systolic pressure and a more pronounced drop in aortic diastolic pressure. The systolic pressure returned toward the control level before tissue sampling No changes in arterial blood pyruvate, lactate or lactate/pyruvate ratio were noted in samples drawn 150 to 180 seconds after beginning beta stimulation and the mean values were not significantly different from those obtained in the control group (see Table I) Analysis of ventricular wall tissue procured after 240 seconds of beta stimulation revealed in an outer to inner wall comparison, that both pyruvate and lactate were relatively higher in the inner wall Such differences were not present in the control group In agreement with the control group however was the lack of an outer to inner wall difference in lactate/pyruvate ratios. Statistical analysis of the ratios was performed by first dividing the lactate value by the pyruvate value for each tissue sample and treating the quotient as an individual statistic. An absolute increase in tissue pyruvate over control values was noted in both regions following

Isoproterenol hydrochloride (Isuprel Winthrop) diluted with saline to yield a concentration of 10 μg per milliliter was infused at a rate of 1 ml per minute into a femoral vein with the use of an automatic syringe pump The drug was prepared from an unopened vial immediately before use.

Blood samples were drawn into chilled glass syringes and precipitated immediately in cold 6 per cent perchloric acid for assay of pyruvate[10] and lactate[11] Additional samples were obtained anaerobically for estimation of Po_2 Pco_2 and pH in a blood electrode system (Instrumentation Laboratories Model 113-S1) Hematocrit was determined on arterial blood Tissue sampling was performed high on the left ventricle slightly lateral to the crux formed by the anterior descending and circumflex branches of the left coronary artery using an electrically driven cutting device fashioned after a cork borer The specimen a transmural tissue plug weighing approximately 5 Gm was quickly transferred to liquid nitrogen Complete sampling time averaged 6 seconds and never exceeded 10 seconds. The frozen specimen was split into approximately equal endocardial and epicardial portions and pulverized in a liquid nitrogen–cooled compression mortar In later experiments the frozen specimen was ground more precisely into equal layers using a specially designed frozen powder mill In a 4 C cold room the weighed frozen powder was transferred to a Potter Elvehjem tube and extracted during grinding with 6 per cent perchloric acid Following centrifugation at 13 000 g for 30 minutes in the cold the clear supernatant fluid was removed Aliquots of both blood and tissue filtrates were analyzed immediately for pyruvate The remaining filtrates were stored in the frozen state and analyzed for lactate later usually within 24 hours All procedures on the filtrates were performed in duplicate or triplicate. Tissue residues were dried to constant weight in an oven for calculation of tissue water content In early experiments tissue water content was also determined on unfrozen samples, which yielded essentially identical results.

Following the experiment the position of the coronary cannula in the main left coronary artery segment was examined to verify patency of the major branches including the septal branch The flowmeter transducers were calibrated with animal blood

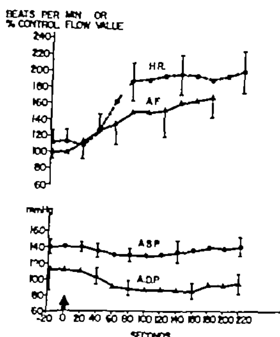


Fig 2 Plots of hemodynamic variables before and during beta stimulation by the intravenous administration of isoproterenol. Circles represent mean values and bars represent standard errors of mean for 10 animals. *HR*, Heart rate *AF* aortic flow *ASP* aortic systolic pressure *ADP* aortic diastolic pressure.

Statistical methods A preliminary investigation of the tissue data revealed that some of the samples had non-Gaussian characteristics that could lead to erroneous conclusions when the t test and other normal theory-dependent procedures were used Therefore nonparametric statistical procedures were used Inner and outer wall differences within each experimental group were investigated by the Wilcoxon matched pairs signed-ranks test.[13] Intergroup differences were investigated by the Kruskal Wallis H test.[13] If the H test gave a statistically significant value ($P < 0.05$) differences between groups were analyzed by the Mann Whitney U test[14] Blood and hemodynamic data were analyzed by these same statistical procedures for making in group comparisons between the control coronary constriction and isoproterenol infusion periods and for making intergroup comparisons between the control and beta stimulated groups.

ble II. Hemodynamic data obtained on coronary constricted animals (mean values and S.E.M 5 control and 9 beta stimulated animals)

	Control group		*Beta stimulated group*		
	Before constriction	*After constriction*	*Before constriction*	*After constriction*	*During beta stimulation*
art rate (beats/min.)	134 ± 11	142 ± 13	137 ± 8	142 ± 9 (0 05)	205 ± 10 (0 01)†
stolic pressure (mm. Hg)					
Aortic	122 ± 9	128 ± 7	133 ± 7	131 ± 7	124 ± 8
Coronary	117 ± 9	106 ± 7	128 ± 7	114 ± 5 (0 01)	85 ± 4 (0 01)†
Difference	5 ± 1	22 ± 4 (0 05)*	5 ± 3	17 ± 3 (0 05)	39 ± 6 (0 01)†
astolic pressure (mm. Hg)					
Aortic	91 ± 7	97 ± 4	101 ± 6	100 ± 6	83 ± 2
Coronary	91 ± 8	66 ± 8	100 ± 6	74 ± 3 (0 01)	38 ± 3 (0 01)†
Difference	1 ± 1	31 ± 5 (0 01)*	1 ± 1	26 ± 5 (0 01)	45 ± 6 (0 05)†
ronary flow (ml./min.)	91 ± 12	85 ± 10	79 ± 3	74 ± 7	119 ± 14 (0 01)†
ronary vascular resistance (units)	1 13 ± 0 17	0 91 ± 0 10	1 26 ± 0 27	0 88 ± 0 14 (0 01)	0 39 ± 0 10 (0 01)†
ronary-ventricular pressure index	2 11 ± 0 11	1 58 ± 0 09	2 11 ± 0 15	1 60 ± 0 08 (0 01)	1 07 ± 0 12 (0 01)†

value for difference after constricting.
value for difference during beta stimulation.

essure, mean aortic flow and mean coronary flow for the entire group of animals dergoing coronary constriction and beta im lation The isolated points at N present values obtained under normal perimental conditions before coronary nstriction. The bars denote standard rors of the mean. The points joined by es represent values obtained after coronary constriction and during beta stimula on with isoproterenol. There was no ange in mean coronary flow following ronary constriction. Thus, the added sistance to flow was not greater than that hich could be actively compensated for by e process of autoregulation The normal sponse of the vessel to partial constriction arteriolar dilatation which in this case as sufficient to keep mean flow constant. he calculated drop in coronary vascular sistance for this group was significant Table II) Beta stimulation caused coronary flow to increase from 74 ± 7 to 119 ± 14 *ml* per minute (61 per cent) at its maximal point.

A previously described numerical index of the pressure-time relationships between the coronary artery and the intraventricu la cavity which correlated with the onset and severity of subendocardial under perfusion was estimated in this group This index, called the coronary ventricular pressure index, was obtained by dividing the area under the coronary artery pressure curve for a cardiac cycle by the area under the ventricular pressure curve during systole. In those experiments in which ven tricular pressure was above base line in diastole, the area under this portion of the ventricular pressure curve was subtracted from the coronary artery pressure curve. It had been shown that below a value of 1.30 deposition of a diffusible substance delivered in the coronary circulation was

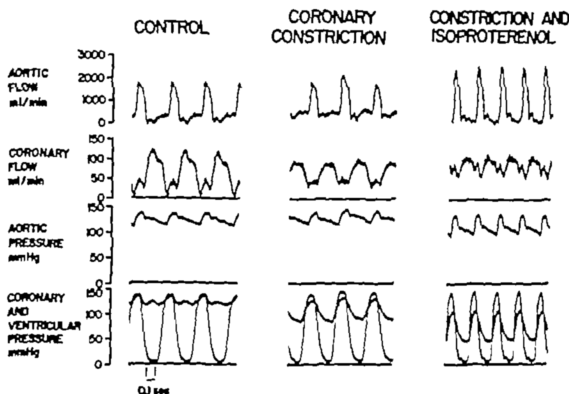


Fig. 3. Illustration of records obtained in one animal before coronary constriction, after coronary constriction, and during coronary constriction plus beta stimulation.

beta stimulation. In spite of this, the lactate pyruvate ratios for outer and inner wall were not different from those obtained in the control group. Tissue water content was uniform for all tissue samples.

Coronary constricted animals. Results were obtained in nine animals in which the main left coronary artery had been cannulated and the cannula tubing partially constricted before beta stimulation. Fig. 3 is an illustration of records obtained in a typical experiment. In the control period no measurable difference existed between peak coronary artery and ventricular systolic pressure, whereas after coronary constriction coronary artery pressure was less than ventricular systolic pressure. Beta stimulation resulted in a further accentuation of this pressure difference and a more marked depression of coronary diastolic pressure. Flow in the cannula became less phasic due to the greater magnitude of the pressure gradient between the aorta and coronary artery in systole. In this experiment, as in the others, ventricular end diastolic pressure did not rise nor did aortic flow decline from its augmented level.

Fig. 4 is a plot of the time course of heart rate, mean aortic pressure, mean coronary

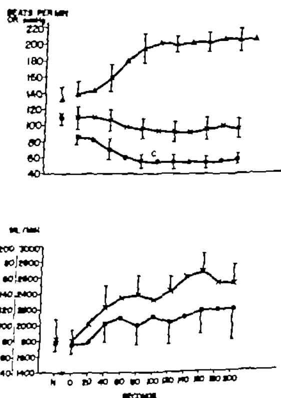


Fig. 4. Plots of hemodynamic variables before and after coronary constriction, and during beta stimulation. 9 animals. N, During normal experimental conditions. HR, heart rate. AP, mean aortic pressure. CP, mean coronary pressure. AF, mean aortic flow. CF, mean coronary flow.

Table II. Hemodynamic data obtained on coronary constricted animals (mean values and S.E.M for 5 control and 9 beta stimulated animals)

	Control group		Beta-stimulated group		
	Before constriction	After constriction	Before constriction	After constriction	During beta stimulation
Heart rate (beats/min.)	134 ± 11	142 ± 13	137 ± 8	142 ± 9 (0.05)	205 ± 10 (0.01)†
Systolic pressure (mm. Hg)					
Aortic	122 ± 9	128 ± 7	133 ± 7	131 ± 7	124 ± 8
Coronary	117 ± 9	106 ± 7	128 ± 7	114 ± 5 (0.01)	85 ± 4 (0.01)†
Difference	5 ± 1	22 ± 4 (0.05)*	5 ± 3	17 ± 3 (0.05)	39 ± 6 (0.01)†
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Aortic	92 ± 7	97 ± 4	101 ± 6	100 ± 6	83 ± 2
Coronary	91 ± 8	66 ± 8	100 ± 6	74 ± 3 (0.01)	38 ± 3 (0.01)†
Difference	1 ± 1	31 ± 5 (0.01)	1 ± 1	26 ± 5 (0.01)	45 ± 6 (0.05)†
Coronary flow (ml./min.)	91 ± 12	85 ± 10	79 ± 5	74 ± 7	119 ± 14 (0.01)†
Coronary vascular resistance (units)	1.13 ± 0.17	0.91 ± 0.10	1.26 ± 0.27	0.88 ± 0.14 (0.01)	0.39 ± 0.10 (0.01)†
Coronary ventricular pressure index	2.11 ± 0.11	1.58 ± 0.09	2.11 ± 0.15	1.60 ± 0.08 (0.01)	1.07 ± 0.12 (0.01)†

*P value for difference after constriction.
†P value for difference during beta stimulation.

pressure, mean aortic flow, and mean coronary flow for the entire group of animals undergoing coronary constriction and beta stimulation. The isolated points at N represent values obtained under normal experimental conditions before coronary constriction. The bars denote standard errors of the mean. The points joined by lines represent values obtained after coronary constriction and during beta stimulation with isoproterenol. There was no change in mean coronary flow following coronary constriction. Thus, the added resistance to flow was not greater than that which could be actively compensated for by the process of autoregulation. The normal response of the vessel to partial constriction is arteriolar dilatation which in this case was sufficient to keep mean flow constant. The calculated drop in coronary vascular resistance for this group was significant (Table II). Beta stimulation caused coronary flow to increase from 74 ± 7 to 119 ± 14 ml. per minute (61 per cent) at its maximal point.

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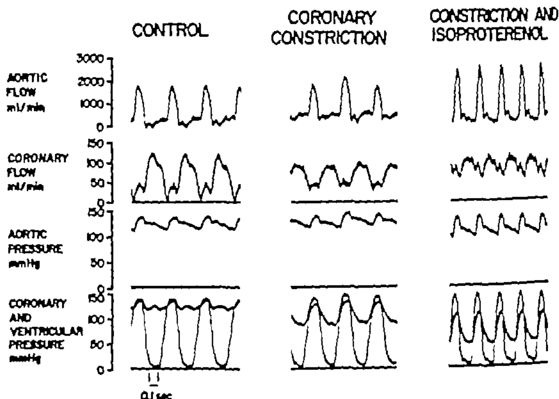


Fig. 3. Illustration of records obtained in one animal before coronary constriction, after coronary constriction, and during coronary constriction plus beta stimulation.

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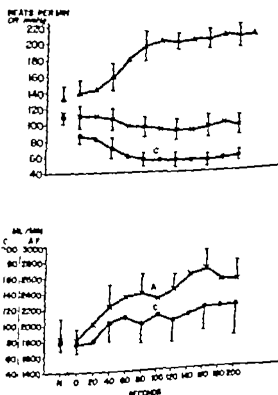


Fig. 4. Plot of hemodynamic variables before and after coronary constriction, and during beta stimulation after coronary constriction. A During normal experiment [illegible] tion in 9 animals. N, During normal conditions. HR, heart rate. [illegible], mean aortic pressure. AF, mean aortic flow. CP, mean coronary pressure. CF, mean coronary flow.

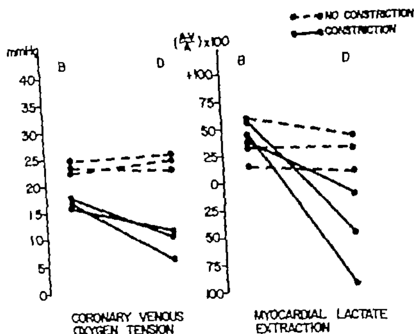


Fig. 5 Plots of coronary venous oxygen tension and myocardial lactate extraction in 3 normal and 3 coronary constricted animals before (*B*) and during (*D*) beta stimulation.

Samples of coronary venous blood were obtained before and during beta stimulation in three normal animals and in three coronary constricted animals. Data on coronary venous oxygen tension and myocardial lactate extraction, defined as the percentage of lactate removed from the arterial blood by the myocardium are illustrated in Fig 5 In the coronary constricted animals the coronary venous oxygen tension declined during administration of isoproterenol whereas in the normal animals it remained essentially constant Likewise in the coronary constricted animals myocardial lactate extraction changed from a positive to a negative value during beta stimulation indicating a reversal of myocardial lactate metabolism from net utilization to net production. Calculation of lactate uptake and release obtained in these three animals by multiplying the arteriocoronary sinus blood difference by the mean coronary flow rate gave a net uptake value of 26.4 ± 3.3 µmoles per minute before beta stimulation and a net release value of 47.0 ± 21 7 µmoles per minute during beta stimulation In contrast to these findings on lactate, pyruvate uptake by the myocardium was increased during beta stimulation in all three coronary constricted animals. Uptake values before and during beta stimulation were 1 43 ± 0 45 µmoles per minute and 2.24 ± 0.45 µmoles per minute, respectively Extraction values were positive in all three of the normal animals.

Discussion

One aim of the present study was to determine whether the subendocardium of the normal left ventricle would exhibit a more anaerobic form of metabolism during beta-adrenergic receptor stimulation It had been shown previously that the subendocardium was more susceptible to ischemia when total left coronary flow was reduced experimentally [4] This was attributed to a relative exclusion of blood flow from the deep myocardium because of the intramyocardial tissue pressure gradient which increases from epicardium to endocardium The possibility that an increase in contractile activity of the ventricle might result in uneven changes in myocardial metabolism because of a greater disparity between oxygen supply and demand in the subendocardium was proposed by Kirk and Honig Their studies suggested to them that the subendocardium was relatively

Table III Arterial blood and tissue data obtained on coronary constricted animals (mean values and S.E.M. for 5 control and 9 beta stimulated animals)

Group	Arterial blood						
	Hct (%)	Po_2 (mm Hg)	Pco_2 (mm Hg)	pH (units)	Pyruvate (mM)	Lactate (mM)	Lactate/pyruvate (mM)
Control							
Before constriction	45 ± 3	77 ± 2	38 ± 1	7 41 ± 0 02	0 114 ± 0 021	0 852 ± 0 323	7 32 ± 2 10
After constriction					0 103 ± 0 013	0 711 ± 0 219	7 04 ± 2 25
Beta-stimulated							
Before constriction	44 ± 2	85 ± 5	35 ± 2	7 42 ± 0 01	0 126 ± 0 018	0 892 ± 0 177	6 76 ± 0 60
During beta stimulation					0 129 ± 0 017	1 448 ± 0 469	7 33 ± 0 90

Group	Outer and inner ventricular wall			
	Pyruvate (μmoles/Gm.)	Lactate (μmoles/Gm.)	Lactate/pyruvate	Tissue H_2O (%)
Control				
Outer	0 102 ± 0 019	0 867 ± 0 159	9 10 ± 1 85	78 1 ± 0 5
Inner	0 131 ± 0 025	0 887 ± 0 227	7 29 ± 1 58	78 0 ± 0 3
Beta-stimulated				
Outer	0 110 ± 0 021	2 220 ± 0 370 (0 02)	25 6 ± 6 44 (0 02)	78 6 ± 0 96
Inner	0 123 ± 0 021	3 952 ± 0 612 (0 002) (0 01)†	36 9 ± 7 21 (0 002) (0 01)†	78 1 ± 0 30

P value for difference between same regions in control group and beta-stimulated group.
†P value for difference between outer and inner wall in beta-stimulated group.

relatively less in the inner than the outer half of the left ventricular wall In the present study the index after constriction but before beta stimulation was 1 60 ± 0 08 well above the critical value but during beta stimulation it dropped to 1 07 ± 0 12 (see Table II)

The control group consisted of five animals which underwent coronary cannulation and constriction without beta stimulation The measured hemodynamic variables before and after constriction paralleled those before and after constriction in the beta-stimulated group The coronary ventricular pressure index before and after constriction were virtually identical in the two groups.

Arterial blood pyruvate lactate and lactate/pyruvate ratio were unchanged by either coronary constriction or coronary constriction plus beta stimulation (see Table III) Tissue analysis revealed that beta stimulation of the coronary constricted animal resulted in a substantially higher lactate level in the inner wall as compared to the outer wall No outer to inner wall difference in pyruvate was found resulting in a higher inner wall lactate/pyruvate ratio In contrast to the effects of beta stimulation in the normal animal there was an absolute increase in tissue lactate rather than pyruvate in both regions This was sufficient to cause the lactate/pyruvate ratios in both outer and inner wall to be above the control values. Tissue water content was constant in both regions.

circumstances. It is conceivable that the most superficial layers of the myocardium continued to utilize blood lactate, since it has been shown[17] that the left ventricle continues to oxidize lactate at a time when net lactate production occurs secondary to a reduction in coronary flow. The degree to which the rise in coronary flow during beta stimulation was attenuated in the coronary constricted animal could not be assessed since it was not possible to obtain total left coronary flow data in the normal animal for comparison. However, data on total left coronary flow were obtained on three coronary cannulated, nonconstricted animals under identical experimental conditions which revealed a 115 per cent increase during beta stimulation in contrast to the 61 per cent increase noted in the cannulated, constricted group.

Since reduced patency of the main stem coronary vessels is a frequent manifestation of human coronary atherosclerosis, the coronary constriction–beta stimulation studies may serve as a useful model of stress-induced coronary insufficiency in man. A preponderance of subendocardial lesions has been cited in autopsy studies on patients who died with the clinical diagnosis of acute coronary insufficiency. Likewise, the elaboration of a network of vessels, called the *subendocardial plexus* has been described in the deep myocardium of coronary heart disease victims.[21,22] An additional clinical complication in acute coronary insufficiency which might accentuate the inner wall metabolic changes is acute left ventricular failure[16] with its attendant increase in ventricular radius and diastolic transmural pressure gradient. One of the beneficial effects of nitroglycerin on exercise hemodynamics[23] may be interruption of such a self-perpetuating process.

Summary

The possibility that the subendocardial region of the left ventricle would exhibit a more anaerobic form of metabolism than the subepicardial region during beta adrenergic receptor stimulation was examined in the open chest dog. The additional effect of reduced coronary vessel patency was also examined. Beta stimulation was achieved by administering isoproterenol intravenously for 4 minutes, after which time a transmural tissue sample was procured from the beating left ventricle for estimating outer and inner wall levels of pyruvate, lactate and tissue water content. Results in the animal with a normal coronary circulation revealed relatively higher inner wall levels of both pyruvate and lactate but no outer to inner wall difference in the lactate/pyruvate ratio. An absolute increase in tissue pyruvate was noted in both regions. Results in the animal with reduced coronary vessel patency revealed a relatively higher inner wall level of lactate but not pyruvate and a higher lactate/pyruvate ratio in the inner than the outer wall. An absolute increase in tissue lactate was noted in both regions. Tissue water content was uniform in all studies. These findings suggest that, although the subendocardial region may be the site of greatest metabolic activity during beta adrenergic receptor stimulation the presence of a normal coronary circulation insures against the development of a more anaerobic form of metabolism there. However, a reduction in coronary vessel patency does predispose the subendocardial region to a more anaerobic form of metabolism during beta-adrenergic receptor stimulation.

The authors wish to acknowledge the help of Dr. Gerald R. Chase of the Department of Statistics and the Department of Community Health who performed the statistical analysis of the data.

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underperfused even in the unstressed heart a conclusion which is supported by some studies[15 16] but not by others[2,3 17 18] In the present study beta stimulation of the normal animal did result in the development of a relatively higher lactate level in the inner ventricular wall although the absolute value was not increased In the absence of additional information such a finding might be construed as biochemical evidence of relative subendocardial underperfusion However pyruvate also was found to be higher in the inner wall in such proportion with lactate that the lactate/pyruvate ratio was not higher in the inner than the outer wall Since it has been demonstrated that the pyruvate level exerts a direct effect on the lactate level and that the lactate/pyruvate ratio is a better index of the oxidation reduction potential of the cell than lactate alone[19] the present findings are against the hypothesis that the left ventricle develops a more anaerobic form of metabolism in the subendocardium during beta stimulation The finding of an absolute increase in pyruvate in both outer and inner wall regions is consistent with other evidence that beta stimulation of the myocardium results in the preferential utilization of noncarbohydrate substances[20] such as fatty acids[21] for oxidative metabolism During increased fatty acid utilization pyruvate entry into the citric acid cycle is reduced[22] because of inhibition of pyruvate dehydrogenase by acetyl coenzyme A and reduced nicotinamide adenine dinucleotide[23] One possible reason for the relatively higher levels of pyruvate and lactate in the inner wall during beta stimulation would be greater energy utilization there There is evidence of increased tension development[8] longer resting length[24] and further shortening distance[25] of sarcomeres located in the deep myocardium Boerth and colleagues[26] found a lower phosphocreatine concentration in the inner wall of the canine left ventricular isovolumic preparation When they increased wall stress by raising ventricular volume a lower adenosine triphosphate concentration was also noted in the inner wall In the present studies increasing the mechanical energy of the myocardium by beta stimulation might well have caused a greater increase in the rate of chemical energy utilization in the inner than the outer wall and hence a more marked change in the pattern of substrate metabolism in the inner wall

In contrast to the above findings in the normal animal in the coronary constricted animal clear-cut evidence of a more anaerobic form of metabolism in the subendocardium than the subepicardium of the left ventricle was found during beta stimulation The lactate and lactate/pyruvate ratio values were substantially higher in the inner wall both on a relative and on an absolute basis There was no increase in tissue pyruvate suggesting the more obligatory role of this substrate as a hydrogen acceptor in the presence of a reduced oxygen tension That tissue oxygen tension was reduced can be inferred from the coronary sinus blood oxygen tension data (Fig 5) Associated with these metabolic events were hemodynamic changes consisting of profound coronary artery hypotension maximal coronary vasodilation and a coronary vent cular pressure index below 1.3 In a previous study[3] such hemodynamic changes were associated with a redistribution of myocardial blood flow away from the inner wall It was presumed that under such conditions the distribution of blood flow was no longer regulated by vasomotion but was dependent upon the intramyocardial tissue pressure gradient which increases from epicardium to endocardium Thus, in the present study the basis for a more anaerobic form of metabolism in the subendocardium may be the combination locally of a relatively higher oxygen requirement due to greater wall stress, and a relatively lower oxygen delivery due to greater coronary extravascular pressure.

Although beta stimulation in the presence of partial coronary constriction resulted in a substantial increase in the myocardial tissue lactate concentration and in net myocardial lactate production there was no evidence of a decline in the augmented aortic blood flow or of a rise in left ventricular end-diastolic pressure at the time of tissue sampling It would thus appear that the process of anaerobic glycolysis was more beneficial than deleterious to over all cardiac function under the

Coronary collateral circulation: Determination of an anatomical anastomotic index of functional collateral flow capacity

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The estimation of functional collateral flow capacity from postmortem injection specimens has been a persistent problem in studies of coronary collateral circulation. Since large intercoronary anastomoses have been demonstrated in certain altered metabolic states of the myocardium -4 in which physiologic indices of collateral flow i.e., peripheral coronary pressure and retrograde flow are elevated it has been assumed that an increase in the anatomic size of the coronary collaterals results in an increased coronary collateral blood flow. However there are two limitations to this assumption i.e. (1) a quantitative anatomic index representing the size and number of intercoronary collaterals in an individual heart was not available for correlation with the physiologic indices (2) the simultaneous measurement of the physiologic and morphologic indices of coronary collateral development in the same experimental subjects was a rarity in previous investigations. Thus, the present study was comprised of the simultaneous measurement of peripheral coronary pressure, retrograde flow and a quantitative anatomic index of coronary collaterals in a random dog population. The latter index was developed by modifying Fulton's anastomotic index to account for Poiseuille's law i.e. the capacity for collateral flow is proportional to the fourth power of the radius of any one collateral, or the total capacity for collateral flow in an individual heart is proportional to the sum of the fourth power of the radii of all anastomoses. The results demonstrate that the quantitative anatomic anastomotic index correlates with the physiologic indices and can be used as an investigative tool in estimating the functional flow capacity of the coronary collateral circulation.

Methods and materials

Studies were carried out in 18 healthy dogs weighing 20 to 35 kilograms. Physiologic indices of coronary collateral flow i.e.

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Studies were carried out in 18 healthy dogs weighing 20 to 35 kilograms. Physiologic indices of coronary collateral flow, i.e.,

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peripheral coronary pressure and retrograde flow were determined in an open-chest anesthetized preparation (11 dogs) and in an intact unanesthetized preparation (7 dogs)

Open-chest anesthetized preparation Eleven dogs were anesthetized with intravenous sodium pentobarbital (30 mg per kilogram of body weight) Supplemental doses were given as needed A left thoracotomy was performed in the fifth left intercostal space while the animal was maintained on intermittent positive pressure breathing with a Harvard respirator The heart was exposed and supported in a pericardial sling The main branches of the left coronary artery were identified and a 1 5 cm segment of either the left anterior descendens or the left circumflex branch was dissected free The animal was heparinized with an initial intravenous dose of 5 mg per kilogram of body weight. Additional doses were given every 30 minutes thereafter Peripheral coronary pressure and retrograde flow were measured by one of the following procedures (1) either the left anterior descendens or the left circumflex branch was ligated with a silk suture and a polyvinyl tube (resistance 0 3 mm Hg per milliliter per minute) was inserted distal to the ligature and securely tied in place (2) a silastic T tube (resistance 0 7 mm Hg per milliliter per minute) was inserted through a small incision in either the left anterior descendens or the left circumflex branch and securely tied in place This latter procedure permitted continuous coronary blood flow until the time of coronary artery occlusion A polyvinyl catheter (resistance 0 37 mm Hg per milliliter per minute) was placed in either the femoral or carotid artery to obtain systemic arterial blood pressure and heart rate Pressures were measured by Elema Schonander pressure transducers and recorded on an Elema-Schonander Mingograf 81 ink jet recorder In the second procedure occlusion of the major arterial branch was maintained for 2 to 3 minutes to obtain peripheral pressure and retrograde flow measurements Following occlusion of the major arterial branch retrograde flow was allowed to drip from the coronary tube which was located on the same level as the right atrium into a graduated cylinder for at least 30 seconds. Peripheral coronary pressure measurements were obtained before and after each determination of retrograde flow After two or more pressure and flow determinations were recorded in each animal it was killed with an overdose of sodium pentobarbital the heart was removed and placed in cold saline in a refrigerator for 24 to 36 hours to await the passage of rigor mortis

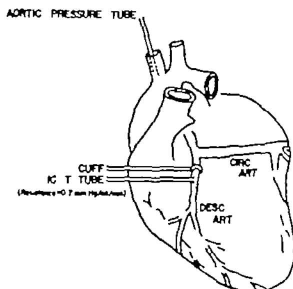


Fig 1 Schematic diagram of heart showing the silastic T tube implanted in the left anterior descendens branch. Pneumatic cuff is proximal to the T tube.

Intact unanesthetized preparation In 3 dogs at the time of thoracotomy a pneumatic occlusive cuff[10] was placed on the left circumflex branch An intracoronary tube[11,12] was implanted in the left circumflex branch distal to the cuff for measurement of peripheral coronary pressure Aortic pressure was measured by a catheter inserted into the distal aortic arch In 4 dogs at the time of thoracotomy a pneumatic occlusive cuff[10] was placed on the left anterior descendens branch and a silastic T tube (Fig 1) inserted in the same branch distal to the cuff The T tube permitted continuous coronary blood flow until the time of cuff occlusion Then measurements of peripheral coronary pressure and retrograde flow were obtained from the T tube These devices were tunneled subcutaneously and attached to appropriate skin connectors Measurements of coronary col

lateral blood flow were conducted after the animals had recovered from surgery, generally 2 to 3 days. Patency of the intracoronary tube was maintained by flushing once or twice daily with 20,000 U.S.P. units per milliliter of heparin while the aortic tube was flushed daily with 1,000 U.S.P. units per milliliter of heparin. Fibrinolysin was occasionally needed to obtain free backflow of blood. After pressure and flow determinations were recorded in each animal for several days, it was killed with an overdose of sodium pentobarbital, the heart was removed and prepared for gelatin injection.

Gelatin injection method. The hearts were warmed to room temperature and the atria removed. The occluded coronary branch was cannulated immediately distal to the occlusion site, while the unoccluded branch was cannulated at its origin with polyethylene tubing. Both major left coronary branches were injected with a modified Schlesinger mass which permitted consistent penetration of arteries to vessels having diameters of approximately 20μ.[1, 11] A different-colored gelatin mass was injected into each major branch. The gelatin mass was injected into both major coronary branches simultaneously. An injection pressure of 150 mm. Hg was maintained for 30 to 40 minutes. The polyethylene cannulas were then ligated. The hearts were then immersed in 10 per cent formalin and allowed to fix for 4 to 5 days. The gelatin-injected specimen was then cleared according to the method of Spalteholz, which was comprised of bleaching with 30 per cent hydrogen peroxide, dehydrating with increasing concentrations of ethanol, and final clearing with methyl salicylate.

Anatomic anastomotic index. After clearing, each heart was cross-sectioned into three equal parts forming the basal, middle, and apical sections. These were then individually examined under a dissecting microscope equipped with a calibrated eyepiece. Intercoronary anastomoses were identified by visualization of vessels filled with gelatin mass which exhibited an intermingling of the different colors injected into the two major left coronary branches. The diameters of individual intercoronary collaterals were determined, and the collaterals were counted and grouped according to the following sizes: 40 to 100μ, 100 to 200μ, and greater than 200μ. Collaterals less than 40μ in diameter were not counted since they are not considered to be functionally significant.[2, 17] In the hearts examined the largest anastomosis observed was 230μ in diameter. Representative sections were taken from the injected specimens for histologic examination.

A quantitative anastomotic index related to capacity for coronary collateral blood flow was determined by application of Poiseuille's law, which states: volume of

$$\text{flow} = \frac{\pi p r^4}{8 u L}$$ where p = pressure gradient,

r = radius, u = viscosity of blood, and L = axial length of the vessel. Accordingly, flow is proportional to the fourth power of the radius which can be multiplied by the number of channels present, to produce an index of total flow. Capacity of flow is then proportional to the fourth power of the radius times the number of collaterals. The maximum radius observed in each group was determined. Its fourth power was obtained and simplified by dividing by 10^6. This factor was multiplied by the number of collaterals in its respective group in order to calculate the anastomotic index. Table I denotes the factors used. The general formula for any one heart comprised the following: total capacity for collateral blood flow is proportional to 6.25 times the number of collaterals 40 to 100μ in diameter plus 100 times the number of

Table I. Determination of an anatomic anastomotic index (AI)

Collateral diameter (μ)	No. of collaterals	Factor† ($radius^4/10^6$)
40-100	A	6.25
100-200	B	100
200-300‡	C	175‡

*AI = 6.25A + 100B + 175C.

†Maximum radius observed in each group used to determine the factor (see Methods in text).

‡Maximum collateral diameter observed in this group was 230μ, thus the radius of 115μ was used to calculate this factor.

Table II. Incidence and size of intercoronary collaterals

Dog	Size of intercoronary collaterals			AI
	40-100μ	100-200μ	200-300μ*	
Anesthetized open chest				
1	1	15	—	1 606
2	20	11	—	1 225
3	15	16	1	1 869
4	15	13	6	2 444
5	24	5	—	1 650
6	10	15	—	1 562
7	—	—	—	—
8	8	16	—	1 650
9	17	17	—	1 806
10	10	1	—	162
11	1	12	2	1 625
Unanesthetized conscious				
12	7	3	—	344
13	18	6	1	888
14	9	4	—	456
15	10	10	4	1 763
16	24	8	3	1 469
17	16	5	—	600
18	14	5	3	1 112

*Maximum collateral diameter observed in this size range was 230μ.

collaterals 100 to 200μ in diameter plus 175 times the number of collaterals 200 to 300μ in diameter. The sum thus obtained is designated the anastomotic index (AI) for an individual heart. Thus for each heart a quantitative index was determined which could be compared with the quantitative values for retrograde flow and peripheral coronary pressure. Appropriate statistical methods with the use of regression analysis and calculation of correlation coefficients were conducted according to the methods of Snedecor.[18]

The AI was compared with another index of coronary collateral development, i.e., collateral vascular capacity devised by Rees and Redding.[19] Since diastolic blood pressure is considered to be the effective perfusion pressure,[20] collateral vascular capacity was obtained by dividing retrograde flow by diastolic aortic blood pressure and was considered to represent the total capacity of the coronary collateral bed.

Since the level of peripheral coronary pressure is dependent on perfusion pressure, i.e., aortic pressure, the values for peripheral coronary pressure were made independent of differences in aortic perfusion pressure in different animals by the use of the ratio of diastolic peripheral coronary pressure over diastolic aortic blood pressure.[16]

Results

The distribution of coronary collaterals in each heart are given in Table II, while the physiologic and morphologic indices of coronary collateral circulation obtained in all animals are presented in Table III. The range of values for retrograde flow, peripheral coronary pressure, and the anatomic AI were similar in the two preparations, i.e., the anesthetized open-chest and the intact unanesthetized animals. Regression analysis was carried out on the complete data obtained in the anesthetized open-chest animals to define the relationship between the various indices. The results are shown in Figs. 2 and 3.

Over the range of observed values there was significant correlation between retrograde flow and diastolic peripheral coronary pressure (r = 0.84). In contrast there was

Table III Physiologic and morphologic indices of coronary collateral circulation

Dog	ABP (mm. Hg)	HR (beats/min.)	DPCP (mm. Hg)	RF (ml./min.)	DPCP/DBP	CVC	AI
Anesthetized, open chest							
1	106	170	12	5.1	0.11	0.061	1.606
2	122	128	11	3.7	0.10	0.034	1.225
3	102	170	7	3.5	0.10	0.050	1.869
4	99	206	20	7.5	0.26	0.106	2.444
5	100	180	12	4.8	0.13	0.056	1.650
6	86	193	12	4.0	0.15	0.050	1.562
7	102	190	8	5.1	0.16	0.050	—
8	93	210	15	4.6	0.20	0.064	1.650
9	99	160	15	4.4	0.17	0.049	1.806
10	96	180	0	—	0.00	—	162
11	123	145	16	4.6	0.14	0.045	1.625
Unanesthetized, conscious							
12	93	150	8	—	0.10	—	344
13	100	119	6	—	0.07	—	888
14	100	145	10	—	0.11	—	456
15	103	137	15	4.0	0.16	0.043	1.763
16	101	180	20	3.3	0.22	0.036	1.469
17	88	108	10	1.8	0.12	0.022	600
18	115	125	16	2.0	0.15	0.019	1.112

Abbreviations: ABP, mean aortic blood pressure; HR, heart rate; DPCP, diastolic peripheral coronary pressure; RF, retrograde flow; DPCP/DBP, diastolic peripheral coronary pressure/diastolic aortic blood pressure; CVC, collateral vascular capacity (retrograde flow ÷ diastolic aortic blood pressure); AI, anastomotic index (see Methods in text).

poor correlation between retrograde flow and either systolic or mean peripheral coronary pressure (r = 0.08 and 0.40, respectively). When values for retrograde flow and diastolic peripheral coronary pressure are adjusted for differences in aortic perfusion pressures between animals with the use of collateral vascular capacity[18] and the ratio of diastolic peripheral coronary pressure over diastolic aortic blood pressure,[20] the correlation between these two indices was greater (r = 0.89) (Fig. 2). Thus, immediately after coronary artery ligation, values for retrograde flow and diastolic peripheral coronary pressure vary directly and are equally reliable indices of each other.

If increases in the physiologic indices of coronary collateral circulation reflect an increase in the anatomic development of coronary collaterals, then collateral vascular capacity and the diastolic peripheral coronary pressure over diastolic aortic blood pressure ratio should show similar correlations with the quantitative anatomic AI. The significant high degree of correlation between collateral vascular capacity and the AI (r = 0.87) is shown in Fig. 3. As expected, a similar high degree of correlation (r = 0.88) existed between the diastolic peripheral coronary pressure over diastolic aortic blood pressure ratio. These results indicate that as the anatomic development of coronary collateral circulation increases, represented by an increased anatomic AI, there is a corresponding increase in the physiologic indices of coronary collateral development.

Figs. 4 and 5 demonstrate gelatin injection specimens from 2 dogs having low and high values for the physiologic and morphologic indices of coronary collateral development. In Dog 2 (Fig. 4) retrograde flow and diastolic peripheral coronary pressure were low. Relatively few intercoronary collateral vessels were present. The ones present were small in size, i.e., two thirds of them were less than 100μ in diameter. In contrast, Dog 4 (Fig. 5) had higher values for retrograde flow and diastolic peripheral coro-

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Fig. 4. Dog 2, gelatin specimen. Although small vessels have filled in the peripheral distributions of both the left circumflex (upper right) and left anterior descendens (lower left) branches, few collaterals communicate between the two vascular beds. (X5.)



Fig. 5. Dog 4, gelatin specimen. In this view of the apex the distal portions of the left anterior descendens (*LAD*) and left circumflex (*LC*) branches are demonstrated. Numerous small and some large intercoronary anastomoses communicate freely between the distal portions of both vascular beds. (X5.)

Discussion

Following coronary artery ligation the primary determinants of collateral blood flow and the transference of the pressure head from the central source (aorta) should be the number and size of intercoronary anastomoses. At the onset of coronary occlusion pressure within the proximal portion of the occluded vessel falls creating a pressure gradient. Dilatation of this distal portion of this vascular bed increases the pressure gradient. Flow into this region comes through existing collaterals from a high pressure source i.e. neighboring unoccluded arteries. According to Poiseuille's law the physical diameter of the collateral vessels becomes the rate-limiting factor of collateral blood flow. Thus the capacity for collateral flow is proportional to the fourth power of the radius of any one collateral and the total collateral capacity in any one heart depends on the sum of the fourth power of the radii of all anastomoses present between the occluded and unoccluded vessels.

Since retrograde flow and peripheral coronary pressure relate directly to aortic perfusion pressure, variations in them apart from those attributable to differences in coronary collateral development may be due to different aortic perfusion pressures. To adjust for differences in aortic perfusion pressure observed in the various animals retrograde flow and peripheral coronary pressure were divided by the aortic blood pressure to yield collateral vascular capacity[13] and diastolic peripheral coronary pressure over aortic blood pressure ratio.[20] Similarity of these ratios in different animals would indicate uniformity of coronary collateral development. The validity of this assumption was confirmed by the data in Table III. In those animals having similar ratios, the AI's were also comparable.

Summary

Following coronary artery ligation retrograde flow and diastolic peripheral coronary pressure are reliable indices of each other and equally dependent on the number and size of interarterial coronary collaterals in accordance with Poiseuille's law. A quantitative anatomic AI has been derived with the use of Poiseuille's law. The AI for an individual heart represents the size and number of coronary collaterals and significantly correlates with the physiologic

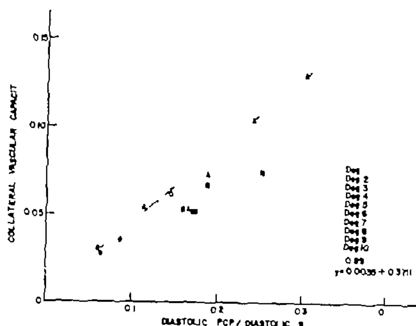


Fig. 2. Relationship between collateral vascular capacity[1] and diastolic peripheral coronary pressure over diastolic aortic blood pressure ratio.[10] Individual observations from different animals are denoted by separate symbols. The regression line is indicated by dotted line.

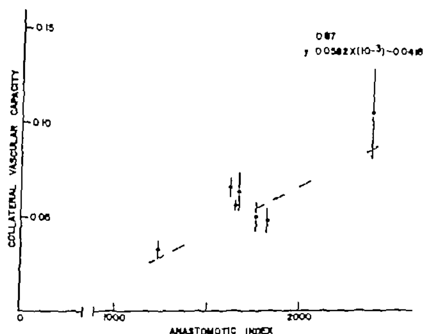


Fig. 3. Relationship between collateral vascular capacity[1] and the number and size of intercoronary collaterals as described by the anastomotic index. Collateral vascular capacity values shown for each animal are means (filled circles) ± standard deviations (vertical lines).

nary pressure. An increased number of intercoronary collaterals were evident over the epicardial surface. More than half of these measured greater than 100μ in diameter.

Although heart rates were lower in the unanesthetized conscious dogs, the range of values for the physiologic and morphologic indices of coronary collateral development were similar to those observed in the intact open-chest preparations (Table III). The correlation between the physiologic indices and the anatomic AI in the unanesthetized conscious animals studied were similar to the detailed ones presented above.



Fig. 4 Dog 2, gelatin specimen. Although small vessels have filled in the peripheral distributions of both the left circumflex (upper right) and left anterior descendens (lower left) branches, few collaterals communicate between the two vascular beds. (×5)



Fig. 5 Dog 4 gelatin specimen. In this view of the apex the distal portions of the left anterior descendens (*LAD*) and left circumflex (*LC*) branches are demonstrated. Numerous small and some large intercoronary anastomoses communicate freely between the distal portions of both vascular beds. (×5)

Discussion

Following coronary artery ligation the primary determinants of collateral blood flow and the transference of the pressure head from the central source (aorta) should be the number and size of intercoronary anastomoses. At the onset of coronary occlusion pressure within the proximal portion of the occluded vessel falls creating a pressure gradient. Dilatation of this distal portion of this vascular bed increases the pressure gradient. Flow into this region comes through existing collaterals from a high pressure source, i.e., neighboring unoccluded arteries. According to Poiseuille's law the physical diameter of the collateral vessels becomes the rate limiting factor of collateral blood flow. Thus the capacity for collateral flow is proportional to the fourth power of the radius of any one collateral and the total collateral capacity in any one heart depends on the sum of the fourth power of the radii of all anastomoses present between the occluded and unoccluded vessels.

Since retrograde flow and peripheral coronary pressure relate directly to aortic perfusion pressure, variations in them apart from those attributable to differences in coronary collateral development may be due to different aortic perfusion pressures. To adjust for differences in aortic perfusion pressure observed in the various animals retrograde flow and peripheral coronary pressure were divided by the aortic blood pressure to yield collateral vascular capacity[1] and diastolic peripheral coronary pressure over aortic blood pressure ratio.[16] Similarity of these ratios in different animals would indicate uniformity of coronary collateral development. The validity of this assumption was confirmed by the data in Table III. In those animals having similar ratios, the AI's were also comparable.

Summary

Following coronary artery ligation retrograde flow and diastolic peripheral coronary pressure are reliable indices of each other and equally dependent on the number and size of interarterial coronary collaterals in accordance with Poiseuille's law. A quantitative anatomic AI has been derived with the use of Poiseuille's law. The AI for an individual heart represents the size and number of coronary collaterals and significantly correlates with the physiologic

indices of coronary collateral development Thus the AI can be used as an investigative tool in indirectly assessing the functional significance of coronary collaterals while conversely retrograde flow and diastolic peripheral coronary pressure are indirect measurements of the anatomic development of the coronary collateral circulation

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Pathophysiology and experimental treatment of acute pulmonary embolism

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Acute obstruction of the pulmonary vascular bed, when induced experimentally by embolism or constriction of the pulmonary artery, is accompanied initially by right ventricular and pulmonary hypertension. If pulmonary vascular obstruction is severe, right heart filling pressure increases while right ventricular systolic pressure, cardiac output, and systemic pressures progressively decrease.[1-6] These changes eventually lead to cardiovascular collapse. Such a sequence of events has been ascribed to acute right ventricular failure resulting from imbalance between right ventricular oxygen demands and right ventricular oxygen supply, which produces an insufficiency of coronary blood flow relative to the demand of the pressure-loaded right ventricle. If such a mechanism were responsible for the hemodynamic findings, then any intervention that decreased right ventricular oxygen demands or increased coronary blood flow to the right ventricle would be expected to produce a salutary hemodynamic effect. The present investigation was undertaken to test this hypothesis by the application of experimental techniques which might provide a prototype for the mechanical treatment of circulatory collapse induced by massive pulmonary embolism. The basic design of the experiment was to produce embolism in dogs, and then to determine the hemodynamic effects of (1) decreasing right ventricular pressure (RVP) work by pulmonary artery counterpulsation[17] and (2) increasing coronary perfusion pressure by balloon occlusion of the descending aorta.

Methods

Nine mongrel dogs weighing 17 to 23 kilograms were subjected to bilateral thoracotomy under pentobarbital anesthesia (35 mg. per kilogram) with positive pressure ventilation (97 per cent O_2, 3 per cent CO_2). After ligation of the hilum of the right lung, the right main pulmonary artery was divided and cannulated for counterpulsation with a Harvard reciprocating piston pump (Fig. 1). The counterpulsation pump was synchronized so that blood was injected into the pulmonary artery in diastole and withdrawn throughout ventricular systole. The stroke of the pump

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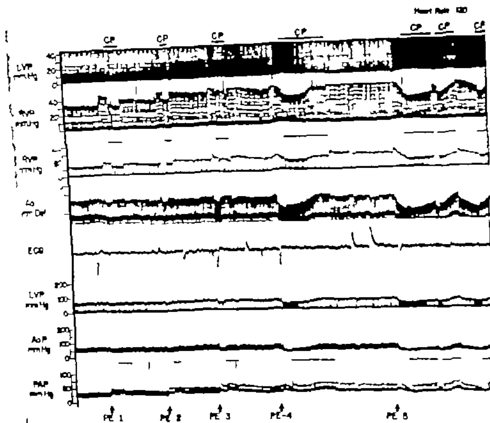


Fig. 2. A representative experiment, recorded at 0.25 mm. per second. From above down are left ventricular pressure (LVP) 0 to 40 mm. Hg; right ventricular pressure (RVP) 0 to 100 mm. Hg; aortic blood flow ($Ao.F$) in millimeters of deflection; electrocardiogram (ECG); left ventricular pressure (LVP) 0 to 200 mm. Hg; systemic arterial pressure ($Ao.P$), 0 to 200 mm. Hg; and pulmonary artery pressure (PAP) 0 to 100 mm. Hg. Thrombus injections (PE 1-5) are associated with incremental increases in pulmonary artery and right ventricular systolic pressure until failure occurs (PE-4). Failure is characterized by falling RVP, LVP, and $Ao.F$. The effect of counterpulsation (CP indicated by horizontal bars) prior to failure consists of reduced right ventricular systolic pressure. After failure (PE-4) counterpulsation restores left and right ventricular systolic pressure and cardiac output toward normal. The preparation is stable when the pump is turned off and failure reappears after embolization (PE 5) and is again reversed by counterpulsation.

Results

The time course of a representative experiment is illustrated in Fig. 2. Injection of thrombus into the innominate vein is associated with incremental increases of systolic pressure in the right ventricle and pulmonary artery while systemic pressure and cardiac output remain constant or decline slightly. The onset of cardiac failure following a series of injections of thrombi is indicated by a rapid and progressive decrease in pulmonary and systemic systolic pressures, a decreasing cardiac output, and an increasing RVEDP. In two animals, no therapeutic intervention was attempted and death ensued by ventricular fibrillation within five minutes from the time circulatory collapse appeared. In the experiment illustrated in Fig. 2 counterpulsation was twice employed to reverse acute cardiac failure due to massive pulmonary embolism (PE-4, PE 5). The effects of counterpulsation in the steady state prior to failure are also indicated.

In all seven animals treated with counterpulsation and in three of the five animals treated with aortic occlusion circulatory collapse was reversed as evidenced by the return of pulmonary and systemic systolic pressures, cardiac output, and RVEDP

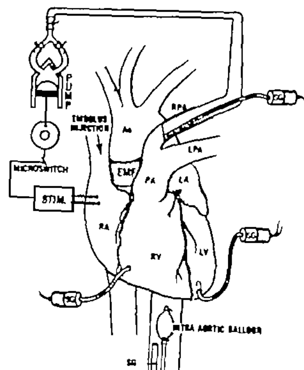


Fig. 1. Experimental preparation. The counterpulsation apparatus consists of a cannula in the right main pulmonary artery connected by tubing to a piston pump. Pump systole triggers stimulator (*STIM*) by a microswitch and cardiac systole is induced by an electrical stimulus delivered to the right atrium. The interval between pump systole and right atrial stimulation is adjustable permitting synchronization. Emboli are introduced into the pulmonary circuit by injection of thrombus into the innominate vein. An inflatable balloon catheter at the level of the diaphragm permits distal aortic occlusion. Pressures in the right and left ventricles and the pulmonary and systemic arteries are measured with cannulas and strain gauges. Aortic blood flow is measured with an electromagnetic flow probe (*EMF*).

was adjusted to provide a withdrawal injection time ratio of 60:40[17,18] and set to deliver its effect on circulatory hemodynamics at a stroke volume of 10 to 20 ml. An inflatable balloon catheter was introduced into the right femoral artery and positioned in the descending aorta at the level of the diaphragm. The sinoatrial node was crushed and the atrium was paced at a rate of 120 beats per minute. The ascending aorta was encircled with an electromagnetic flow probe.* Statham P23Db strain gauges were employed to measure pressure through cannulas in the right and left ventricles, the main pulmonary artery, and the left femoral artery. The flowmeter was calibrated by cardiac output measurements determined by the indicator dilution method. Arterial blood gases, hematocrit, and body temperature were monitored and maintained within physiologic limits. Prior to the experiment, polyvinyl tubing of ¼ inch internal diameter was filled with fresh homologous canine blood which was allowed to clot and which was refrigerated overnight. The tubing was cut to 20 cm. lengths, each containing approximately 14 ml. of thrombus. Portions of the enclosed thrombus were introduced incrementally through a cannula into the innominate vein until cardiac failure supervened.[4]

Failure was considered to be present whenever right ventricular systolic pressure, which initially increased with injection of a thrombus, began to fall progressively. This change was associated with an increase in right ventricular end-diastolic pressure (RVEDP) and decreases in aortic flow (Ao F), aortic pressure (Ao P), and left ventricular systolic pressure. Irreversible circulatory collapse was considered to be present when the above changes progressed to the point that aortic systolic pressure fell to 50 mm. Hg or less. Pulmonary artery counterpulsation or occlusion of the descending thoracic aorta by inflation of the catheter balloon with saline were applied individually in random order when cardiac failure as just defined was present. Circulatory stability usually was re-established after about 5 to 10 minutes of treatment. At this point counterpulsation or balloon occlusion was discontinued and failure was allowed to recur. If failure did not recur spontaneously, additional emboli were injected. The effects of the therapeutic interventions were then further assessed. In this fashion counterpulsation was evaluated in all seven animals; balloon occlusion was evaluated in five. The usual time during which counterpulsation or balloon occlusion was employed was 5 to 10 minutes, although counterpulsation was successfully employed for up to 40 minutes and balloon occlusion for 15. Total duration of preparation and experimentation was less than 3 hours. Statistical significance of experimental results was established by the use of paired t tests.

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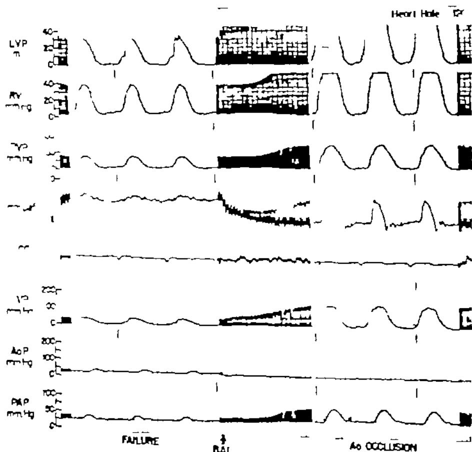


Fig. 4 Effects of distal aortic occlusion on embolism-induced failure. Legend as in Fig. 2. Inflation of the aortic balloon (BAL) damps the distal arterial pressure trace (A P) and is associated sequentially with an increase in left ventricular systolic pressure and stroke volume (LVP A F) an increase in right ventricular systolic pressure and decrease in RVEDP

ative of acute right ventricular failure. Aortic occlusion raises central aortic pressure in the face of a very low cardiac output by reducing distal runoff of the blood ejected from the left ventricle. The elevated central aortic pressure presumably leads to an increase in coronary blood flow and myocardial function is thereby improved. These observations help to differentiate two alternative hypotheses which can be invoked to explain the circulatory collapse that occurs during massive pulmonary embolism. One theory holds that the sudden increase in outflow resistance causes the right ventricle to become overdistended failure occurs because the ventricle is functioning on the descending limb of its function curve. This mechanism would not appear to explain right ventricular failure induced under the experimental conditions of the present investigation since circulatory collapse consistently occurred at a RVEDP of 6 mm Hg or less, and end diastolic pressures of as much as 10 to 15 mm Hg are easily tolerated by the canine right ventricle during an acute volume load.[9] Moreover other investigators have demonstrated that withdrawal of blood under similar experimental circumstances leads to a deterioration of cardiac function whereas a salutary effect would be expected to occur if the heart were functioning on the descending limb of the ventricular function curve.[8] In addition prior transfusion improves the capacity of the right ventricle to withstand subsequent pulmonary arterial occlusion.[4,11] Finally electron microscopic observations of normal

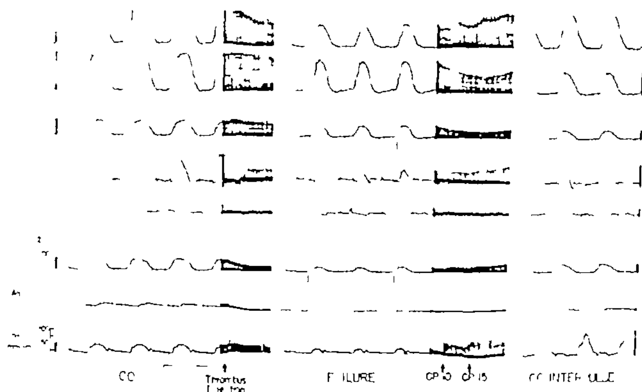


Fig. 3. Effects of counterpulsation on cardiac failure induced by pulmonary embolus. Legend as in Fig. 2. Control tracing on the left shows pulmonary hypertension induced by prior embolization. An additional injection of thrombus causes progressive reductions of systolic pressures in right and left ventricles and aortic blood flow. RVEDP rises, and left ventricular end-diastolic pressure falls. Counterpulsation at a stroke volume of 10 ml. (*CP 10*) produces increased pulse pressure in the pulmonary artery (*PAP*), right ventricular unloading, and some increase in left ventricular systolic pressure. Increasing stroke volume to 15 ml. (*CP 15*) produces large pressure pulses in the pulmonary arteries and restores other hemodynamic parameters toward prefailure values.

toward prefailure values. In many instances it was noted that when aortic occlusion or counterpulsation was discontinued after being employed to treat an episode of circulatory collapse the hemodynamic status of the animal remained reasonably stable. Representative illustrations of these effects of counterpulsation or of increased aortic resistance are presented in Figs. 3 and 4. The results are detailed in Tables I and II and summarized in Fig. 5. Both interventions caused gradual increases in left ventricular systolic pressure and cardiac output, and a decrease in RVEDP. Maximal hemodynamic improvement occurred after 2 to 4 minutes. Recovery from circulatory collapse with balloon occlusion was associated with a significant increase in right ventricular systolic pressure; this was not observed during counterpulsation because of the unloading action of the pump. In addition, balloon occlusion of the aorta produced a greater augmentation of left ventricular systolic pressure than that observed during counterpulsation. Otherwise the hemodynamic effects of balloon occlusion and counterpulsation were similar.

At the onset of circulatory collapse a small decrease in left ventricular end-diastolic pressure (LVEDP) frequently was observed. When this decrease occurred it always immediately preceded the downward spiral of left and right ventricular systolic pressures and cardiac output.

Discussion

The present results indicate that both pulmonary artery counterpulsation and occlusion of the aorta with a balloon catheter can effectively reverse otherwise fatal cardiovascular collapse in animals subjected to experimental pulmonary embolism. Counterpulsation reduces the pressure work of the right ventricle, an effect that leads to reversal of the hemodynamic changes indic

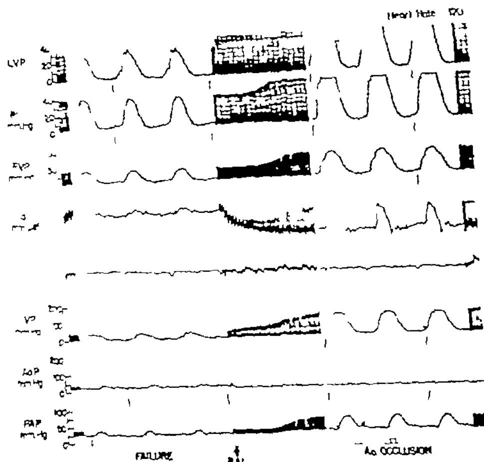


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Table I. Hemodynamic effects of pulmonary embolism and circulatory alterations produced by pulmonary counterpulsation

	Pressure (mm Hg)				Cardiac output (L./min.)	Aortic pressure (mm Hg)	Pulmonary artery pressure‖ (mm Hg)
	RVEDP	RVP	LVEDP	LVP			
Controls							
PE-3	1	27	4	75		75/45	30/15
PE-4	0	36	3	150	1 36	120/65	38/15
PE-5	1	35	2	70	1 70	60/50	42/23
PE-6	3 5	33	4	75	2 57	50/30	40/20
PE-8	2	32	5	80	0 87	90/55	20/12
PE-9	1	32	3	75	0 77	80/45	38/15
PE-10	3	33		95	0 81	95/70	45/25
Mean	1 6	32 6	3 3	88 6	1 34	81/51	36/18
S.E.	0 5	1 1	4	10 7	0 26		
Prefailure							
PE-3	4	65	2	70		75/40	67/38
PE-4	4	62	2 5	115	0 98	75/35	62/28
PE-5	3	70	4	90	2 59	98/70	4/40
PE-6	4 5	62	3	70	2 57	55/30	65/38
PE-8	2	50	2	65	0 87	70/40	50/28
PE-9	3 2	55 5	9	82 5	1 28	6/48	62/28
PE-10	5 5	64	1	82 5	0 68	80/52	70/42
Mean	3 7	61 2	2 5	82 1	1 50	76/45	64/35
S.E.	0 4	2 5	0 4	6 4	0 35		
†P	< 0 01	< 0 01	NS	NS	NS		
Failure precounterpulsation							
PE-3	6	32	6	42		30/22	42/30
PE-4	5	35	3 5	50	0 34	42/25	36/22
PE-5	10	60	2	45	0 82	40/30	65/40
PE-6	5	60	2	37	0 23	20/15	65/38
PE-8	2	32	3	38	0 42	35/20	38/25
PE-9	5 8	35	0 8	30	0 38	27/21	38/23
PE-10	9 6	41	0 7	38	0 28	58/28	51/40
Mean	6 2	42 1	2 6	40 0	0 41	36/20	48/31
S.E.	1 1	4 7	0 7	2 4	0 09		
‡P	< 0 05	< 0 01	< 0 01	< 0 01	< 0 05		
Counterpulsation recovery							
PE-3	2	47	4	75		70/35	62/30/25
PE-4	1 25	18 5	3	70	0 88	60/32	68/18/8
PE-5	7	60	5	105	4 17	115/75	100/60/28
PE-6	3	31	4	55	1 95	37/20	108/38/31
PE-8	1	20	4	66	1 07	65/35	100/25/18
PE-9	3	34 6	3 7	68 6	1 36	60/35	114/23/20
PE-10	3 3	38 3	2 3	78 3	0 83	75/50	97/48/37
Mean	2 9	35 6	3 7	74 0	1 71	58/40	93/35/24
S.E.	0 8	5 5	0 3	5 9	0 52		
§P	< 0 01	NS	NS	< 0 01	< 0 05		

RVEDP, Right ventricular end-diastolic pressure; LVEDP, left ventricular end-diastolic pressure; RVP, right ventricular peak systolic pressure; LVP, left ventricular peak systolic pressure; S.E., standard error of mean.

†Statistical comparison of controls and prefailure.

‡Statistical comparison of prefailure and failure state.

§Statistical comparison of failure and counterpulsation recovery.

‖Pulmonary artery pressure during counterpulsation is given as [illegible] systole/ventricular systole/low point of diastole.

Table II Hemodynamic effects of pulmonary embolism and circulatory alterations produced by balloon occlusion of the aorta

	Pressure* (mm. Hg)				Cardiac output (L./min.)	Aortic pressure (mm. Hg)	Pulmonary artery pressure (mm. Hg)
	RVEDP	RVP	LVEDP	LVP			
Failure prebaloon							
PE 5	6	41	5	50	1.76	45/35	48/15
PE-6	4	50	2	38	0.60	20/15	55/38
PE-6	3	55	2	37	0.42	20/12	62/35
PE 10	6	38	1	35	0.21	35/23	48/35
PE 10	5	40	2	45	0.34	45/30	50/38
PE 10	5	30	2	45	0.22	50/35	40/32
Mean	5.2	42.3	2.3	41.7	0.39	36/25	50/32
S.E.	0.31	3.6	0.6	2.4	0.24		
Balloon recovery							
PE 5	4	55	6	90	2.79	50	62/32
PE-6	4	75	2	75	1.47	7	80/40
PE-6	3	78	2.5	75	1.66	5	82/40
PE 10	3	75	2	135	.74	15	80/42
PE 10	3	58	2	115	.53	15	65/42
PE-10	3.5	43	2	125	.49	20	65/38
Mean	3.4	64.0	2.8	102.5	1.28	19	72/39
S.E.	0.20	5.8	0.7	10.6	0.36		
†P	< 0.01	< 0.01	NS	< 0.01	< 0.02		

*See footnote to Table I.
†Statistical comparison of failure and balloon recovery.

canine right ventricles also suggest that sarcomere lengths present at end-diastolic pressures of 8 mm. Hg or less be on the ascending limb of the length–tension curve.[30]

As an alternative hypothesis, it has been postulated that the markedly increased pulmonary pressure resulting from an acute elevation of pulmonary resistance produces an imbalance between the oxygen requirements and oxygen supply of the right ventricle. The resulting ischemia leads to a depression in myocardial contractility. Such an imbalance could result from one or more interrelated changes. First, delivery of blood to the right ventricle might be insufficient to maintain adequate right ventricular function under the circumstances of a sudden and large increase in right ventricular pressure and consequent increase in oxygen requirements. Second, a reduction in right ventricular output due to elevated resistance to outflow would reduce left heart filling and decrease left ventricular output. This in turn would cause systemic arterial and coronary perfusion pressure to fall, leading eventually to a decrease in coronary blood flow. A vicious cycle would thereby be established: the decrease in coronary flow would lead to a further depression in right ventricular function and a further reduction in left heart filling would lead to further decreases in coronary flow. Finally, it has been suggested[14] that since much of the blood perfusing the right ventricle drains via the Thebesian system into the right ventricular cavity, the marked increase in right ventricular systolic pressure present after massive pulmonary embolism would decrease the pressure gradient between the coronary arteries and right ventricle during systole and might thereby compromise the delivery of that portion of total coronary flow that occurs during systole.[31] Experimentally, coronary blood flow has been shown to increase initially in the steady

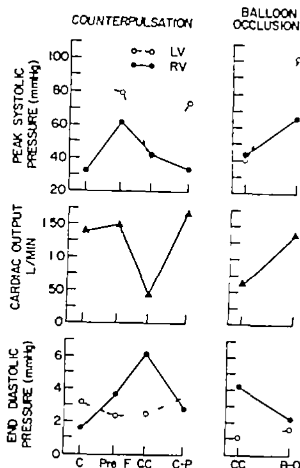


Fig. 5. Graphic summary of experiment 1 results. *LV* Left ventricle *RV* right ventricle *C* control *Pre F* pre failure *CC* circulatory collapse *C-P counterpulsation B-O balloon occlusion of the abdominal aorta.*

state following embolism or pulmonary artery constriction.[23,24] An actual decrease is apparently not observed until cardiovascular collapse supervenes.[24] Nevertheless an absolute increase in coronary flow does not negate the possibility of relative coronary insufficiency since the increase in oxygen demand may exceed the increase in oxygen supply.

It is apparent that while counterpulsation of the pulmonary artery might produce beneficial effects if failure resulted either from overdistension of the right ventricle or from relative myocardial ischemia the beneficial hemodynamic effects of aortic occlusion must principally ameliorate *myocardial ischemia* which thus appears to be a major cause for the circulatory collapse following massive pulmonary embolism. The importance of the fall in systemic pressure in these circumstances was suggested initially by Virchow[23] who noted pathologic evidence of acute myocardial ischemia in death from pulmonary embolism. Subsequently Fineberg and Wiggers[9] observed that when the pulmonary artery of dogs was progressively *constricted* systemic arterial pressure began to fall just at the time the right ventricle manifested signs of failure. Similar conclusions were drawn several years later by Megibow and colleagues[8] and by Salisbury[15] who demonstrated that acute right *ventricular failure* produced by pulmonary arterial constriction could be reversed by external compression of the descending aorta a maneuver that would elevate coronary perfusion pressure. It was subsequently shown[11] that rapid intra-arterial *infusion of blood sufficient to elevate* aortic pressure also succeeded in reversing the circulatory collapse occurring after a massive pulmonary embolus in dogs. In contrast expansion of the blood volume by *intravenous* infusion of blood was completely *ineffective under similar circum*stances.

The present results cannot resolve the controversy surrounding possible reflex effects in massive embolism which may increase pulmonary resistance constrict the coronary arteries reduce systemic resistance or directly depress contractility through withdrawal of sympathetic tone to the heart.[2,4,9,10,12,16] In some experiments in the present study a small decrease in LVEDP immediately preceded the onset of myocardial deterioration suggesting that in those animals a reduction of left ventricular filling was the precipitating cause of failure. In many animals, however no such decrease was observed and either cumulative ischemia or reflex changes might be causally implicated in the onset of failure. While it is thus possible that reflex mediated changes in coronary vascular resistance or myocardial contractility may play a role in the development of circulatory collapse the progressive fall in systemic and thus coronary perfusion pressure are undoubtedly also of great importance.

Although pharmacologic methods have been employed clinically to maintain systemic or to decrease pulmonary arterial pressures in pulmonary embolism many

patients prove unresponsive to all such interventions. The results of this study indicate that mechanical methods employed to support the circulation may be of value under such circumstances. In this connection it is of note that a brief interval of counterpulsation or aortic occlusion frequently restored circulatory stability so that support could be withdrawn without subsequent deterioration (Fig 2) This effect might be due to subsidence of an unfavorable reflex change or reduction of pulmonary resistance through dislodgment of emboli or redistribution of pulmonary vascular perfusion It should be pointed out however that while maintenance of central aortic pressure by a balloon catheter inflated in the abdominal aorta might be applied clinically with one or another of the existing balloon catheters and thereby possibly produce favorable effects on the course of a patient with circulatory collapse due to massive pulmonary embolism it would not be feasible to apply to the clinical situation the specific technique used in this study to counterpulse the pulmonary artery The major practical defect in such a system is the hemolysis that usually accompanies the rapid withdrawal and reinfusion of blood in counterpulsation systems when prolonged support is necessary It is also possible that prolonged counterpulsation could lead to intimal hemorrhage and even frank rupture of the pulmonary artery Further studies are necessary to determine whether pulmonary artery counterpulsation can be successfully employed using a balloon catheter

In conclusion although two mechanical circulatory support techniques have been shown to be effective in the treatment of circulatory collapse following experimentally produced pulmonary embolization it remains to be determined whether they can be adapted to the clinical situation and whether they will offer any advantage over currently employed pharmacological methods.

Summary

Although massive pulmonary embolism can lead to acute circulatory collapse it is not known if the right ventricle fails because it cannot respond to further increments in filling pressure (descending limb of the Starling curve) or because coronary perfusion is inadequate to support its greatly augmented pressure work. Accordingly the effects of mechanical reduction in right ventricular pressure work by pulmonary artery counterpulsation and elevation of coronary perfusion pressure by balloon occlusion of the abdominal aorta were assessed when cardiovascular collapse was induced in open-chest dogs by pulmonary embolism In all seven dogs tested failure was reversed by pulmonary artery counterpulsation. Right ventricular end diastolic pressure fell from 6 ± 1 to 3 ± 1 mm. Hg left ventricular systolic pressure increased from 40 ± 2 to 74 ± 6 mm Hg and cardiac output increased from 0.4 ± 0.1 to 1.7 ± 0.6 L. per minute ($p < 0.05$) In three of five dogs tested failure was similarly reversed by balloon occlusion of the descending thoracic aorta. These findings are consistent with the view that cardiovascular collapse during massive pulmonary embolism is a consequence of relative coronary insufficiency which can be reversed either by an increase in coronary perfusion pressure or by a reduction of the pressure work of the right ventricle

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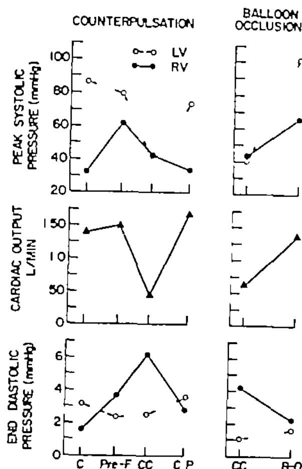


Fig 5 Graphic summary of experimental results. *LV* Left ventricle *RV* right ventricle *C* control *Pre-F* pre failure *CC* circulatory collapse *CP* counterpulsation *B-O* balloon occlusion of the abdominal aorta

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The effects of coupled and paired ventricular stimulation following acute myocardial infarction in dogs

Raul E. Falicov, M.D.
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Chicago, Ill.

Cardiac pump failure following acute myocardial infarction remains largely an unresolved therapeutic challenge. In spite of important advances in other areas of coronary care, the results of available methods of treatment of the low output–cardiogenic shock syndrome are still disappointing. Paired or coupled ventricular stimulation have been suggested by some[1,2] as potentially useful interventions in selected patients presenting with this syndrome, because of their powerful positive inotropic effects. Despite these theoretical advantages, others have questioned the use of paired ventricular stimulation in patients with acute myocardial infarction because of the increased myocardial oxygen requirements produced by this intervention and because of the increased risk of ventricular fibrillation being induced in the acutely ischemic heart.[3] There is little information available regarding the effects of coupled ventricular stimulation on myocardial failure following acute cardiac infarction.

In *paired* ventricular stimulation, the first pulse overdrives the heart and is followed by mechanical contraction; the second is timed to occur in the relative refractory period and causes electrical depolarization without an associated mechanical contraction. The refractory period is prolonged, the ventricular rate slowed and complete atrio-ventricular dissociation maintained. In contrast, when *coupled* ventricular stimulation is undertaken, a single electrical impulse is applied in the relative refractory period following the R-wave of a naturally occurring impulse to depolarize the ventricle without an associated mechanical contraction; the spontaneous beat which follows finds the atrio-ventricular junction refractory and the heart rate is slowed. Whereas both paired and coupled ventricular stimulation effectively slow the heart, normal atrio-ventricular sequence is preserved with coupled ventricular stimulation and the hemodynamic benefit of atrial systole is maintained. Post-extrasystolic potentiation occurs with both techniques.

This investigation was undertaken to assess the hemodynamic effects of coupled and paired ventricular stimulation in an experimental model of acute myocardial infarction associated with myocardial depression in the closed-chest dog.

Methods

Ten mongrel dogs, whose weights varied from 24 to 30 kilograms were anesthetized with sodium pentobarbital (25 mg per

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Coronary embolization was followed by significant decreases in heart rate (10 per cent) cardiac output (48 per cent) stroke volume (44 per cent) aortic pressure (20 per cent) LV dp/dt (36 per cent) and LV stroke work (60 per cent) and minute work (55 per cent) Significant increases in systemic vascular *resistance* (54 per cent) and pulmonary vascular resistance (59 per cent) were recorded Variable changes were recorded in LV end-diastolic pressure (LVEDP) slight increases following em*bolization in 4 animals (LVEDP* <7 mm Hg) and definite increases to abnormal values in the remaining 5 (LVEDP <20 mm Hg) a large left ventricular a wave was identified in this latter group as the cause for the increased LVEDP

R wave coupled ventricular stimulation resulted *in halving the effective ventricular* rate and this was associated with a significant increase in LV dp dt aortic systolic pressure increased in 7 animals remained unchanged in one and decreased in *one There was no correlation between the* magnitude of the postembolic pressure decrease and the pressor response to coupled ventricular stimulation Although end-diastolic aortic pressure decreased during coupl*ed* stimulation there was *little* change in mean aortic pressure Pulmonary arterial pulse pressure also became wider without significant change in the mean pressure Although stroke volume and LV stroke work increased cardiac output and LV minute work remained low and only *slight changes from the postembolic levels* were recorded In a similar fashion LVEDP changed slightly during coupled stimulation other than one animal in whom LV pressure changed from 110/16 to 125/9 *during coupled* stimulation but this was not associated with any improvement in the cardiac output

Paired ventricular stimulation which was maintained successfully in 6 animals caused widening of both aortic and pulmonary arterial pulse pressure without any significant change in their mean values increased in LV dp/dt stroke volume and stroke work occurred but minute work remained at their depressed postembolic levels. Of the 5 animals whose LVEDP had become abnormally elevated following coronary embolization only 2 could be successfully pair paced and in both the *LVEDP decreased from 18 to* 10 and from 14 to 10 mm Hg respectively This reduction in LVEDP was due in the main to the loss of the LV a wave for paired ventricular stimulation causes atrioventricular dissociation LVEDP remained unchanged during paired stimulation in the 4 animals in whom normal values persisted after coronary embolization

Discussion

Selective mercury embolization of the left *circumflex coronary arterial bed in the* dog was first shown by Lluch and coworkers[7] to produce a progressive state of myocardial depression resulting in circulatory collapse and death within 5 to 48 *hours. The course of this animal model re*sembles in many ways the syndrome of cardiogenic shock following acute myocardial infarction in man and the technique has been found effective and reproducible by others.[8] *In our hands,* severe myocardial depression could be consistently produced by embolization of either the circumflex or the anterior descending coronary vascular beds or areas of both vascular *beds follow*ing a single mercury injection into the left coronary artery

The association of a low stroke output elevated end-diastolic pressure decreased systemic arterial pulse pressure and intense systemic arterial vasoconstriction observed in this preparation at the time of study does represent an experimental counterpart to the clinical syndrome of low output failure following acute myocardial infarction.[9] A brisk elevation in systemic vascular resistance persisted throughout the experiment as a response to the decreased cardiac output and prevented the development of severe hypotension observed in *the fully developed syndrome of* cardiogenic shock in man

Numerous reports have documented that the mammalian heart responds to coupled and paired electrical stimulation *of the ventricles with* a sustained and marked enhancement of its contractile state. This effect becomes particularly noteworthy when a state of myocardial depression or failure has been first

induced in both the heart lung and intact animal preparation.[3, 11] Coupled ventricular stimulation will enhance ventricular contractility and increase aortic flow in normal dogs[13] and after myocardial depression induced by beta adrenergic blockade.[13]

The study of the effects of paired ventricular stimulation on myocardial depression due to acutely induced ischemia has been seriously hampered by the very high incidence of ventricular fibrillation associated with this intervention.[3] This effect is most likely a consequence of the reduced threshold to fibrillation present in the acutely ischemic heart with the combined effect of an increased myocardial oxygen consumption and net myocardial potassium loss caused by the paired stimulation.[13] Little information is available, therefore, in the literature to indicate whether any hemodynamic benefit might be obtained by paired ventricular stimulation in the low-output–cardiogenic shock state following acute myocardial ischemia. Recently Rothfeld and his co-workers have shown that bretylium (5 mg per kilogram) protected 9 of 10 dogs against ventricular fibrillation during paired ventricular stimulation following coronary artery ligation and suggested that the combination of bretylium and paired ventricular stimulation might be therapeutically beneficial in the patient with acute myocardial infarction complicated by cardiogenic shock or low output failure. Our data suggest that, even if the dysrhythmia inducing properties of paired ventricular stimulation could be prevented by drug administration, little or no hemodynamic benefit could be expected from paired ventricular stimulation

The effects of coupled ventricular stimulation on the low cardiac output syndrome following acute myocardial infarction were studied in 7 patients by Gourgon and coworkers. Four patients responded favorably with improvement in consciousness, increased urine flow and blood pressure no significant response was observed in 2 patient and in the last patient, coupled pacing could not be instituted due to failure to stimulate the ventricles. Cardiac output was not measured in any of the patients. In one patient, recurrent ventricular tachycardia was produced by the technique but ventricular fibrillation was not provoked in any All patients who responded favorably to coupled stimulation had high initial heart rates, and part of the favorable response undoubtedly could be attributed to slowing of the excessively rapid heart rate.

We have been unable to find any study recording the effects of coupled ventricular stimulation following experimental myocardial infarction. Our experience indicates that coupled ventricular stimulation, despite preserving atrial systole and increasing myocardial contractility and performance as shown by an increased peak LV dp/dt, stroke volume, and stroke work fails to exert any beneficial influence upon the depressed circulatory state, for the total cardiac output and minute work did not improve nor did the elevated LVEDP respond significantly It might be postulated that this failure to respond was rate related since the heart rate decrease of 50 per cent induced by coupled ventricular stimulation might of itself have been detrimental to the circulation and therefore have offset the increased stroke volume and work produced by coupled stimulation. It is, therefore conceivable that when acute myocardial ischemia is associated with a rapid tachycardia, coupled ventricular stimulation may yet prove to be of significant value by its over all enhancement of myocardial performance.

Our observations indicate that paired ventricular stimulation is ineffective as an inotropic intervention and that furthermore it may be dangerous, for there is a high risk of precipitating ventricular fibrillation its use in man to improve circulatory depression associated with myocardial infarction under these circumstances is probably contraindicated. In contrast, coupled ventricular stimulation is less risky and simpler to maintain but appears ineffective in improving the circulatory state unless a disproportionate tachycardia is present.

Summary

Circulatory depression was produced in 10 anesthetized dogs following left coro-

nary embolization with mercury. Marked decreases in cardiac output and LV dp/dt and significant increases in systemic vascular resistance and left ventricular end diastolic pressure were observed. Systemic arterial pressure decreased only moderately. Coupled and paired ventricular stimulation both resulted in significant increases in LV dp/dt, stroke volume, and stroke work, but cardiac output, LV end diastolic pressure, and systemic vascular resistance remained unchanged. Ventricular fibrillation occurred in one instance during coupled ventricular stimulation and in 6 instances during paired ventricular stimulation.

It is concluded that neither coupled nor paired ventricular stimulation provides significant hemodynamic benefit to the depressed circulatory state following coronary embolization in the dog. Furthermore, the high incidence of ventricular fibrillation contraindicates the use of paired ventricular stimulation during acute myocardial ischemia. Coupled ventricular stimulation may have a beneficial effect when disproportionate tachycardia is present.

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Case reports

Repetitive multifocal paroxysmal atrial tachycardia with cyclic Wenckebach phenomenon under observation for thirteen years

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Parkinson and Papp[1] in 1947 drew attention to the benign prognosis of repetitive paroxysmal tachycardia. Subsequently, Case[2] reviewed only 11 cases, from the year 1900 to 1967, with repetitive supraventricular tachycardia which demonstrated no heart disease. Abrams and Eaddy have described a case with repetitive and multiple ectopic beats.

More recently, Shine, Kastor and Yurchak[4] and Phillips, Spano and Burch[5] described 32 cases and 31 cases, respectively, of what they called multifocal atrial tachycardia or chaotic atrial mechanism among about 12,000 electrocardiograms (ECGs). These authors emphasized high mortality rates and serious complications.

There is much controversy concerning this type of arrhythmia with respect to the presence of organic heart disease and prognosis. This report presents a case of atrial tachycardia with repetitiveness and multiplicity of ectopic beats. It is of particular interest that paroxysms have continued over 13 years observation.

Case report

A 39-year-old Japanese woman had received biennial routine physical examinations at the Atomic Bomb Casualty Commission[6] in Hiroshima since the age of 25 in 1956. She was exposed to the atomic bomb of 1945 at a distance of 2,950 M. from the hypocenter (estimated total radiation dose, 0 rad).

The patient's past history revealed measles and mumps in infancy. In 1949 she was found, during the course of her first pregnancy, to have an irregular radial pulse. During her second pregnancy in 1954 she had appendicitis and tolerated the appendectomy well. In 1956 she had her last delivery without complication.

From 1949 to 1969 she reported, in spite of arrhythmia, no serious or chronic complaints other than mild palpitation with acute respiratory infection.

She weighed 50 kilograms; height was 155 cm. Although the patient was carefully examined from 1956 to October, 1969, the only physical abnormality found was arrhythmia. No heart murmur was audible. Each ECG showed complicated arrhythmia of similar nature (Fig. 1). Auricular rates from 1956 to 1969 ranged from 115 to 136 beats per minute, mostly over 130, and ventricular rates, from 90 to 122 beats per minute. Blood pressures taken in the sitting position were around 110/70 mm. Hg during that period. No pulse deficit was noted. She had not been treated because of freedom from complaints.

Laboratory data including complete blood counts, urinalysis, serology, stool guaiac, and chest roentgenograms were within normal limits at each clinic visit. Serum cholesterol was 176 mg. per 100 ml. A one-hour postprandial blood sugar was 126 mg. per 100 ml. Protein-bound iodine (PBI) was 3.5 μg

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nary embolization with mercury Marked decreases in cardiac output and LV dp/dt and significant increases in systemic vascular resistance and left ventricular end diastolic pressure were observed Systemic arterial pressure decreased only moderately Coupled and paired ventricular stimulation both resulted in significant increases in LV dp/dt stroke volume and stroke work but cardiac output LV end diastolic pressure and systemic vascular resistance remained unchanged Ventricular fibrillation occurred in one instance during coupled ventricular stimulation and in 6 instances during paired ventricular stimulation

It is concluded that neither coupled nor paired ventricular stimulation provides significant hemodynamic benefit to the depressed circulatory state following coronary embolization in the dog Furthermore the high incidence of ventricular fibrillation contraindicates the use of paired ventricular stimulation during acute myocardial ischemia Coupled ventricular stimulation may have a beneficial effect when disproportionate tachycardia is present.

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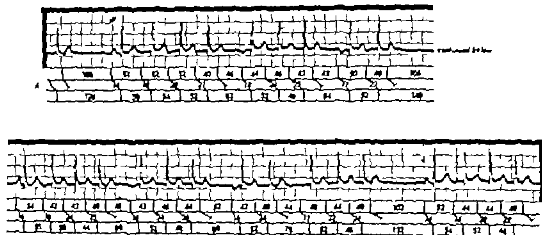


Fig. 2 A continuous ECG strip of Lead II. Single sinus beats following longer ventricular pauses, separating paroxysms, are repeated every 6.2 to 7.7 seconds. The 3:2 and 4:3 Wenckebach phenomenon are repeated 3 to 4 times. The configuration of ectopic P waves is variable and the P-P interval is irregular. These facts suggest repetitive and multifocal atrial tachycardia.

beats were noted every 6.2 to 7.7 seconds (Fig. 2). Each cyclic sinus beat initiated another run of paroxysmal supraventricular tachycardia.

The question is raised whether or not negative P waves (in all limb and precordial leads) preceding the first ventricular complex after the shorter pauses, might well represent either (1) left atrial rhythm, (2) A-V nodal origin with retrograde conduction, or (3) coronary sinus origin. But it is probably true that stimuli causing negative P waves came from the most caudal part of the right atria in this case.

Discussion

The concept of a benign course is supported by the present case in which there were three uneventful pregnancies despite arrhythmia. Even without antiarrhythmic therapy other abnormalities were not found on regular physical examinations over 13 years. Indeed, considering the early history paroxysms appear to have continued for about 20 years. It seems that a relative slowness of the ventricular rate has kept the patient from being disabled.

The present subject most probably developed tachycardia during pregnancy. However the etiologic relation between repetitive tachycardia and pregnancy has not been proved.

Very few cases of repetitive tachycardia with Wenckebach phenomenon have been reported. Moreover cyclic P-R prolongation of the Wenckebach type sustained for long years, as in the present case has never been reported.

The average onset age in repetitive tachycardia with benign prognosis is about 25 years.[3] A high risk of sudden death associated with chaotic atrial mechanism and multifocal atrial tachycardia, has been reported in the average ages of 68.5 and 74 years respectively.[4] The present author speculates that this disparity in clinical courses might well be, in part, accounted for by the great difference in age at discovery. Thus, coronary arteriosclerosis may be a seminal factor leading to the poor prognosis at older ages. However it should be noted that earlier studies put more stress on repetitiveness of ectopic beats than on multiplicity of P waves which was the major criterion of the more recent reports.[4] The present case had both of these characteristics as illustrated in Fig. 2.

Further investigation of the pathophysiologic and etiologic mechanisms is required for full clarification.

Summary

A patient with repetitive multifocal paroxysmal atrial tachycardia with cyclic Wenckebach phenomenon is described. The arrhythmia has persisted, without other physical or laboratory abnormalities, for 13 years and perhaps for about 20 years.

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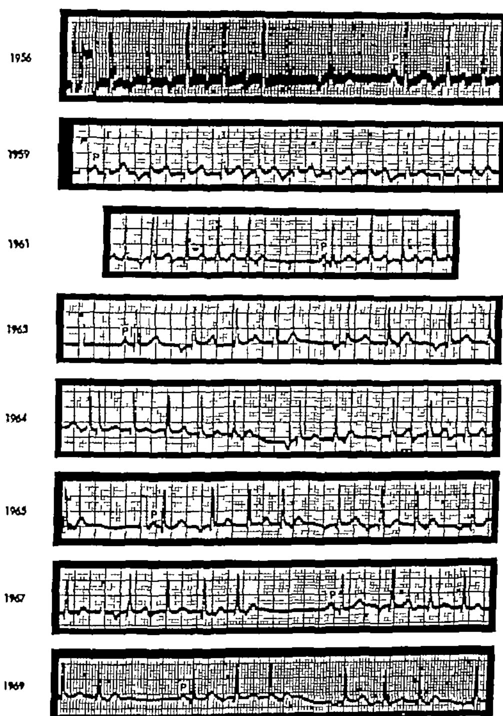


Fig. 1. Serial ECG strips of Lead II from the year 1956 to 1969. The longer ventricular pauses and shorter ventricular pauses within ectopic atrial beats of the 3:2 to 5:4 Wenckebach type, as shown in Fig. 2, are clearly seen through the years. The strips from 1956 and 1959 show longer periods of tachycardia.

per 100 ml (normal 3.5 to 8.0). There was no sign of diabetes or hypothyroidism.

Electrocardiograms. ECG tracings are illustrated in Figs. 1 and 2. A continuous run of regular sinus rhythm was never recorded in any lead at any time.

All the QRS complexes seem to be preceded by P waves, either upright or negative. The P-R interval of the normal sinus beat is 0.16 second. The P-R interval of the periods of ectopic beats are progressively prolonged from 0.16 to 0.17 second to 0.24 to 0.26 second until finally the last P waves fail to be followed by a ventricular complex at the end of each sequence. This then is considered to be incomplete atrioventricular block of the Wenckebach type.

There seemed to be two clearly different pauses, that is (1) shorter ventricular pauses within the bout of rapid rhythm corresponding to single dropped ventricular responses of the Wenckebach type and (2) longer ventricular pauses (without atrial activity) separating paroxysms, usually terminated by single sinus beats. Typically single sinus



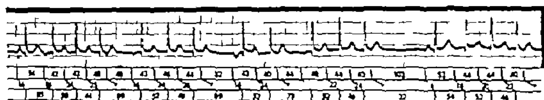


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J. L. Belsky, T. L. Robertson, Y. Ito and S. Wada of the Atomic Bomb Casualty Commission. In addition the author thanks Mr. K. B. Noble and Mr. G. Day for their assistance in the preparation of this report.

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Increase in threshold to ventricular activation related to atrial contraction

A possible example of "Wedensky inhibition

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George Diamond M.D
Los Angeles Calif

Wedensky effect, facilitation and inhibition are electrophysiologic phenomena originally described in nerve muscle preparations. These phenomena have been invoked in the interpretation of the mechanisms underlying certain cardiac arrhythmias. -4 Recently possible examples of both Wedensky effect and facilitation have been described in the human heart.[1-4] Although examples of Wedensky inhibition have not been published Fisch and Greenspan[3] state that the concealment of conduction in cardiac tissue may prove to be similar to if not identical with the Wedensky inhibition seen in nerve tissue

The purpose of this report is to demonstrate examples of inhibition of ventricular activation related to atrial depolarization, a phenomenon which may represent Wedensky inhibition.

Definitions

Wedensky effect may be defined as the enhancement of a subthreshold stimulus by a preceding strong stimulus enabling the subthreshold stimulus to evoke a response.

Wedensky facilitation may be defined as a decrease in the threshold of excitation distal to an area of block as a result of an impulse occurring proximal to the area of block.[4]

Wedensky inhibition may be defined as an increase in the threshold of excitation distal to an area of block as a result of an impulse occurring proximal to the area of block.

Case report

A 55-year-old man was hospitalized on Dec 15 1969 with acute inferior posterior myocardial infarction. A transvenous pacing catheter was inserted per the basilic vein because of advanced A V block (Fig 1) On Dec. 17 1969 Intermittent pacemaker malf nction was noted with stimulus intensity set at 2.0 mA t rate of 67 per minute Chest -ray revealed the catheter tip to be well positioned at the apex of the right ventricle. The following electrocardiographic phenomena were noted

Possible "Wedensky inhibition"

Junctional pacemaker Five nstances were observed of exit block of a junctional pacemaker without interruption or resetting of its cycle (Fig 2) Immediately prior to pacemaker nsertion and at the time the pacemaker was turned off there was ad

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Increase in threshold to ventricular activation related to atrial contraction

A possible example of "Wedensky inhibition"

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Wedensky effect, facilitation, and inhibition are electrophysiologic phenomena originally described in nerve muscle preparations. These phenomena have been invoked in the interpretation of the mechanisms underlying certain cardiac arrhythmias.[1-4] Recently possible examples of both Wedensky effect and facilitation have been described in the human heart.[5-8] Although examples of Wedensky inhibition have not been published, Fisch and Greenspan[3] state that the concealment of conduction in cardiac tissue may prove to be similar to, if not identical with, the Wedensky inhibition seen in nerve tissue.

The purpose of this report is to demonstrate examples of inhibition of ventricular activation related to atrial depolarization, a phenomenon which may represent "Wedensky inhibition."

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Case report

A 55-year-old man was hospitalized on Dec. 15, 1969, with acute inferior posterior myocardial infarction. A transvenous pacing catheter was inserted per the basilic vein because of advanced A-V block (Fig. 1). On Dec. 17, 1969, intermittent pacemaker malfunction was noted with stimulus intensity set at 2.0 mA. at a rate of 67 per minute. Chest x-ray revealed the catheter tip to be well positioned at the apex of the right ventricle. The following electrocardiographic phenomena were noted.

Possible "Wedensky inhibition"

Junctional pacemaker. Five instances were observed of exit block of a junctional pacemaker without interruption or resetting of its cycle (Fig. 2). Immediately prior to pacemaker insertion, and at the time the pacemaker was turned off, there was ad

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Fig. 1 Complete electrocardiogram obtained on Dec 17 1969 demonstrating acute inferior myocardial infarction with A V dissociation Atrial rate is 73 to 86 (ventriculophasic sinus arrhythmia) with junctional rhythm *at 48 to 50 per minute. Exit block from the junctional focus is noted in Lead II when the R P interval is 570* msec.



Fig 2 Exit block of junctional focus related to atrial activation.

Rhythm is advanced A V block with si us rhythm varying between 75 and 82 per minute (ventriculophasic sinus arrhythmia) and junctional pacemaker at 50 per minute. Transient 2:1 exit block of the junct onal focus is noted

Whenever a P wave followed a QRS complex by 570 to 600 msec. there was failure of conduction of the next junctional impulse

vanced A V block with atrial rate 73 to 86 per minute (ventriculophasic sinus arrhythmia) and junctional pacemaker at a rate of 48 to 50 per minute. No evidence of capture beats was noted in the limited strips analyzed Nine P waves occurred within 555 to 600 msec. following the QRS and following five of them there was failure of conduction of the next junctional impulse which should have appeared 610 to

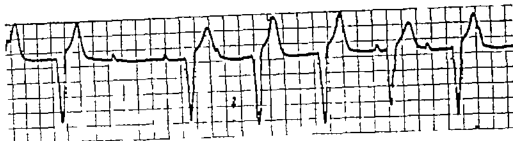


Fig. 3 First and second degree pacemaker ventricular block related to trial activation.
A transvenous right ventricular catheter pacemaker set t 2.0 Ma. activates the ventricles t rate of 67 per minute. The second pacing artifact fails t activate the ventricles. The onset of a P wave precedes this pacing stimulus by 100 msec. The fifth QRS complex is aberrant and ventricular activation is delayed 40 msec. following the pacemaker artifact representing first degree pacemaker ventricular block.
Only hen P wave preceded the pacing stimulus by 80 to 100 msec. was ventricular activation inhibited or delayed. Increasing the intensity of the pacemaker tim lus to 5.0 mA. resulted in normal ventricular activation by all pacemaker impulses.

Table I Relationship of R P interval to suppression of junctional pacemaker

R-P interval (msec)	complexes		% Total suppressed
	suppression	S ppression	
<555	40	0	0
555-600	4	5	55% ($p < 0.005$)
>600	30	0	0

Table II Relationship of R P interval to ventricula pacemaker response (at 2.0 mA)

R P interval (msec)	No. complexes			% Total with aberrant or no response
	Normal ventricular response	ventricular re ponse	Aberrant ventricular response	
785-805	3	8	6	82% ($p < 0.005$)
<785 or >805	442	0	0	0

620 msec after the P wave (Table I)

Art ficial ventricular pacemaker When ever a P wave preceded the pacemaker stimulus by 80 to 100 msec ventricular activation by the pacemaker was either slightly delayed (30 to 40 msec.) and aber rant or totally inh bited (Fig 3 and Table II) Eight instances f inh bition and six of delay and aberration of ventricula response were noted at a time when the pacemaker was set at a rate of 67 per minute (R R 900 msec.) At all other P wave–pacemaker stimulus intervals, pacemaker activation was normal at a stimulus intensity of 2.0 mA. with a threshold of 1.8 mA. When the intensity of the pacemaker stimulus was increased to 5 0 mA. all pacemaker im pulses were conducted irrespective of rela tionship to P waves.

Discussion

Inhibition f junctional pacemaker Fig. 2 is consistent with a parasystolic junctional focus with exit block secondary to con cealed conduction of the preceding P wave. However the remainder of the tracing does not support a parasystolic focus. It is more likely that the junctional rhythm is an es

cape rhythm Concealed conduction would therefore have been expected to result in discharge and resetting of the nonprotected junctional focus Failure to do so would imply that the P wave did *not penetrate* to the level of the junctional pacemaker but in some manner resulted in increased threshold to excitation in the area around the junctional focus thus resulting in exit block This was *not* seen with I waves occurring at R P intervals of less than 555 msec or greater than 600 msec It is therefore suggested that this represents an example of increase in threshold to exit of a junctional pacemaker secondary to atrial activation an effect which may be termed Wedensky inhibition Another possible explanation is that the junctional impulse by means of Wedensky effect and or facilitation allows deeper penetration of the I wave and thereby blocks the escape pacemaker [9]

Artificial ventricular pacemaker The failure or delay and aberration of ventricular pacing whenever a I wave preceded the pacemaker stimulus by 80 to 100 msec implies an inhibitory effect on ventricular activation by the atrial impulse The delay between the pacemaker artifact and the aberrant ventricular response may be considered an example of first degree pacemaker ventricular block with the totally blocked beat representing second degree block

The altered sequence of ventricular activation as seen in Fig 3 is thought to represent aberration rather than fusion because of the very short I R interval (80 to 100 msec) and because of failure of atrioventricular conduction at R P intervals less than 1200 msec when the pacing rate was slowed

I reston[11] has reported the demonstration of an interval following atrial depolarization during which suprathreshold stimuli failed to excite the heart in 11 of 33 patients with complete heart block and ventricular pacemakers and invoked decremental conduction as a possible mechanism

It is possible that catheter motion secondary to atrial contraction could account for an increase in the threshold to ventricular activation since 80 to 100 msec is within the range of delay usually noted between atrial activation and effective mechanical contraction Although this possibility cannot be ruled out it obviously would not explain the inhibition of the *junctional* pacemaker related to atrial depolarization

An alternative explanation is that the atrial depolarization potential resulted in an electrotonic effect which in some manner acted to increase the threshold to stimulation at the pacemaker–right ventricular junction resulting either in inhibition or delay and aberration of the ventricular response

Hodgkin [1] using an isolated nerve preparation has demonstrated that an increase in excitability distal to an area of block following a nerve impulse proximal to the block is related to an extrinsic potential dependent upon the spread of electrotonic current This experiment would explain the phenomenon of Wedensky facilitation Critical timing may determine whether the net effect of the extrinsic potential is an increase or decrease in excitability resulting either in facilitation or inhibition

Summary

First and second degree pacemaker ventricular block and second degree exit block of a junctional pacemaker are demonstrated in relationship to atrial depolarization in a 55 year-old man with acute inferior myocardial infarction and impaired atrioventricular conduction It is proposed that atrial depolarization resulted in a transient increase in threshold of excitation distal to the area of block and thus represents a possible example of Wedensky inhibition

We wish to thank Dr Leonard Dreifus and Leo Schamroth for their ma y helpful uggestions In critically reviewing the manuscript and Dr James P ne for allowing to evaluate th patient

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Acquired right ventricular outflow tract obstruction

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It is not unusual for complicated aneurysms of the ascending aorta to affect left ventricular function Processes causing or associated with an aneurysm may narrow the coronary artery ostia and produce myocardial ischemia or infarction the aneurysm may distort the aortic valve ring and produce aortic insufficiency with subsequent left ventricular hypertrophy dilatation and failure However an unusual manner in which an aortic aneurysm can lead to heart failure is by right ventricular outflow tract obstruction Here the clinical picture often resembles that of pulmonic stenosis.

This report describes such a complication of an aortic aneurysm and focuses attention on the variety of mechanisms by which acquired right ventricular outflow tract obstruction may be produced

Case report

A. D (UMMC 084202) a 57 year-old Caucasian housewife, was admitted Sept. 14 1961 because of chronic back and chest pain. She had sustained fractures of the left clavicle nd the left lower extremity in an automobile ccident 12 years earlier and since then had noticed an intermitt t left subscapula ache which did not l mit activity I 1960 she was refused employment because of a chest x-ray abnormality Five m nths prior to admission the pain increased i frequency nd severity It radiated to an area beneath the left breast nd varied with position and respiration. It did not resemble typical angina pectoris. She also experienced dyspnea on mild exertion and three episodes of transient lightheadedness. She had not had syncope or hemoptysis. There was no history of rheumatic fever venereal disease or heart murmur

The blood pressure was 130/80 mm. Hg and the pulse rate 86 w th a regular rhythm The trachea wa in the midline and the neck veins were not distended in the supine position. The carotid artery pulses were normal The lungs were clear The heart was not enlarged A prominent left parasternal lift was present, but there were no thrills. The second sound spl t physiologically A Grade 3/6 harsh systolic ejection murmur wa present over the entire precordium b t wa loudest in the third tercostal pace at the left sternal border It radiated to the neck, left axilla and the l ng bases. There were no diastolic murm rs. The per pheral pulses were nor mal nd equal bilaterally Cyanosis cl bbl g and edema were absent.

The hematocrit was 37 per cent and the wh te cell count was 4 700 with a normal differential The serology was negati .. A fasting blood sugar was 81 mg per cent the urea nitrogen 18 mg per cent, and cholesterol 189 mg per cent The total serum protei wa 7 8 mg per cent, with an lbumin-glob lin ratio of 1 2.

X-ray examination (Fig 1) revealed a 10 cm calcified thoracic aneurysm which h d increased 1 cm i size since a chest film take six months earlier Electrocardiograms (Fig 2) showed ncom plete right bundle branch block, the S Q T pattern and symmetrical T wave i ersion in Leads II III F and V . An i travenous ngiogram was done with serial biplane filming The right trium was normal. The right ventricle was moderately enlarged The pulmonic valve and the common pulmo-

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nary artery were normal. The left pulmonary artery did not visualize and the right pulmonary artery was compressed at its origin (Fig. 3). The caliber of the vessels on the right beyond the partial obstruction appeared increased. The pulmonary veins, left atrium, left ventricle and ascending aorta appeared normal. There was a large saccular aortic aneurysm of the arch distal to the left subclavian artery which was almost completely filled with laminated clot. The remainder of the aorta was normal. A right heart catheterization was performed (Table 1) and showed right ventricular and common pulmonary artery hypertension with a 60 mm. Hg pressure gradient at the bifurcation of the common pulmonary artery. Cineangiocardiograms demonstrated slowing of the circulation through the right side of the heart. The common pulmonary artery appeared "kinked." The remainder of the study confirmed the findings of aortography.

On the seventeenth hospital day a left thoracotomy was performed. The aneurysm measuring 10 cm. at its greatest diameter and 4 cm. at its base, was dissected free of the lung surface. An attempt was made to isolate the aorta above and below the aneurysm. However these manipulations further compromised the already partially obstructed pulmonary outflow tract and resulted in a decrease in systemic arterial pressure. It became necessary to use cardiopulmonary bypass during which diffuse bleeding began. When clot was evacuated from the aneurysm, the left pulmonary artery began to pulsate vigorously. The aneurysm was excised from the anterolateral aspect of the aorta and replaced by a Teflon graft. However despite all measures, the diffuse bleeding became more severe and the patient died in the operating room.

Discussion

The pulmonary artery arises from the infundibulum of the right ventricle behind the sternal end of the second left intercostal space. It is about 5 cm. in length and 3 cm. in diameter in the adult and is entirely enclosed within the fibrous pericardium. It passes upward and backward while curving through the mediastinum from a position in front of the ascending aorta to a position left of the aorta. Anywhere along this path a vascular, neoplastic, or inflammatory lesion can compromise the outflow tract, masquerade as pulmonic stenosis and produce right ventricular failure.

The early clinical finding of acquired right ventricular outflow tract obstruction is a systolic ejection murmur accompanied by a thrill over the upper left sternal border. The murmur may be continuous (machinery-like) and resemble that of patent ductus arteriosus. Such a murmur in the presence of a thoracic aortic aneurysm is suggestive of acquired right ventricular



Fig. 1. Chest roentgenogram showing calcified thoracic aortic aneurysm.

Table I. Results of right heart catheterization

Site	*Pressure (mm. Hg)*
RA	7/0 (mean 4)
RV	82/19
HRV	75/5
RPA	20/10

Peak systolic pressure gradient at bifurcation of pulmonary artery—60 mm. Hg.
RA = right atrium; RV = right ventricle; HRV = high right ventricle; RPA = right pulmonary artery.

outflow tract obstruction.[1,2] The electrocardiogram is helpful if it shows increasing right axis deviation and other signs compatible with right ventricular hypertrophy. Chest pain and dyspnea are common presenting symptoms.

The most common lesion producing acquired right ventricular outflow tract obstruction is an aortic aneurysm, particularly a syphilitic aneurysm.[3-11] The concave surface of the ascending aorta is a common site for the aneurysm which may enlarge anteriorly and to the left and deform the lumen of the pulmonary artery. In 1839 Hope[12] described a patient with an aortic aneurysm which ruptured into the pulmonary artery. Peacock[13] in 1868 and Kap-

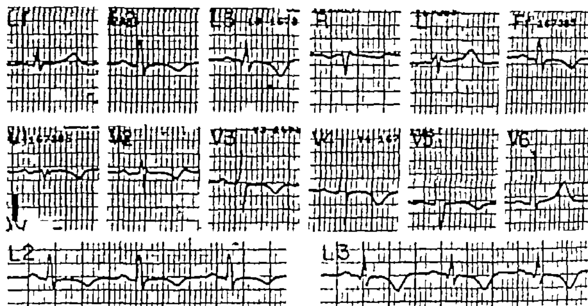


Fig. 2. Electrocardiogram demonstrating findings which may be the result of right ventricular hypertension (incomplete right bundle branch block, S Q T pattern, and symmetrical T wave inversion in Leads II, III, I, and V1.)



Fig. 3. Intravenous angiogram revealing large saccular aortic aneurysm of the arch distal to the left subclavian artery totally obstructing the left pulmonary artery and compressing the origin of the right pulmonary artery.

pis[17] in 1907 each reviewed the literature and reported 19 and 32 similar cases respectively. The signs and symptoms of the rupture of an aortic aneurysm into the right ventricular outflow tract were summarized by Porter[18] and Nicholson[19] and each of these authors presented the clinical picture as a syndrome associated with syphilitic aortitis. Brill and Jones[20] cited 87 patients of whom 84 (96.5 per cent) came to medical attention at the time of rupture of a syphilitic aneurysm into the pulmonary artery. Only 3 (3.5 per cent) of this group had symptoms due only to compression of the right ventricular outflow tract. A nonsyphilitic aortic aneurysm presenting in the latter fashion is an even rarer occurrence. Yacoub and associates[21] presented one such case and another is reported in this paper.

Neoplasms rank second in frequency among the lesions producing right ventricular outflow tract obstruction. Primary intracardiac tumors which have been observed to compromise the right ventricular outflow tract included rhabdomyosarcoma,[22-24] fibrosarcoma,[25] chondrosarcoma,[26] reticulum cell sarcoma,[27] myxoma,[28,29] pleomorphic sarcoma,[3] and mesothelioma of the pericardium.[30] The only reported metastatic intracardiac lesion which has produced this type of obstruction is a malignant argentaffinoma.[31] Extracardiac tumors which have mechanically obstructed the pulmonary artery include teratoma,[2,32] Hodgkin's disease,[33] thymoma,[34,35] and bronchial carcinoma.[1]

An annular constricting pericardial band is the most frequently encountered inflammatory lesion producing acquired obstruction. Gouley[36] described five instances of rheumatic pericarditis which resulted in

supravalvular pulmonic stenosis. Mounsey[47] and McGaff and associates[48] have reported patients with subvalvular obstruction due to a pericardial band. Barros and Gomez[49] described a patient with a pericardial band constricting the right ventricular outflow tract and noted that a partial pericardiectomy had antedated the acquired obstruction in his patient and in those mentioned above. Seymour and coworkers[3] discussed a similar patient with right ventricular outflow tract obstruction after incomplete pericardiectomy. Weglicki and colleagues[50] reported one case of acquired pulmonic stenosis due to a pericardial band without previous pericarditis or pericardial surgery.

Chronic fibrous mediastinitis,[51,52] miliary tuberculosis,[53] and callus formation of the sternum[54] are other inflammatory lesions which have produced right ventricular outflow tract obstruction.

Although acquired right ventricular outflow tract obstruction is an unusual cause of right ventricular failure, it is not such a rare postmortem finding that the clinician should not keep the possibility high on the list of conditions to be considered when he is faced with the inexplicable and gradual onset of right ventricular failure—particularly when this is associated with a new ejection murmur along the upper left sternal border.

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Clinical pathologic conference

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Clinical history

A 45-year-old Negro male schoolteacher had apparently been in his usual state of good health until one month prior to admission to the Medical College of Virginia Hospital. He had first noted the onset of shortness of breath on exertion which became progressively more severe over a one-week period and was unassociated at any time with chest pain. Because of these symptoms he consulted his local physician and was started on a course of penicillin therapy for "bronchitis." Two days following this office visit, he had the sudden onset of chills and fever and progressive orthopnea and was hospitalized in his local community. Upon his admission to the community hospital, the temperature was 100.2° F., pulse, 100, respirations, 24, and blood pressure, 100/80. The tonsils were enlarged and appeared mildly infected. The heart was enlarged; there was a regular rhythm. Decreased breath sounds were present at the right lung base posteriorly, and the liver was palpable two fingerbreadths below the right costal margin. A chest x-ray revealed generalized cardiac enlargement, and the electrocardiogram (ECG) showed left axis deviation and sinus tachycardia. The white blood count (WBC) was 15,200; hemoglobin, 16 Gm. per cent; and urinalysis, normal. Antistreptolysin O (ASO) titer was 25 Todd units and the blood urea nitrogen (BUN) was 41 mg. per cent. Heterophil was negative and throat culture demonstrated heavy growth of beta-hemolytic streptococcus.

The patient was treated with penicillin and digitalis and became afebrile, but the cardiac failure became progressively more severe. Acute rheumatic carditis was diagnosed, and the patient was started on a course of steroid therapy. This treatment was discontinued, however, after the ASO titer was reported to be normal. The steroid dosage was gradually decreased, but the patient showed rapid clinical deterioration in his cardiac status and was transferred to the Medical College of Virginia Hospital.

Review of systems. This was noncontributory.

Family history. The father died at age 58 with mitral insufficiency. The mother was living and said to have primary heart disease. She had undergone cardiac catheterization at a university center approximately five months prior to the patient's admission. One maternal aunt was also said to have heart disease. No family history of diabetes, hypertension, bleeding diathesis, or disorders of the liver was present.

Social history. The patient consumed approximately half a pint of whisky each week day and drank more heavily on weekends.

Physical examination. The temperature was 98.6° F.; the blood pressure (BP) was unobtainable; the pulse was also unobtainable; the respirations were 16 per minute and labored. The patient was a well-developed, well-nourished, drowsy Negro man who was oriented but in moderately severe respiratory distress. The extremities were cool, and the nailbeds were mildly cyanotic. No peripheral blood pressure was present; pulses were not palpable. The apical rate was 110. There was scleral icterus. The neck veins were full without paradoxical filling. The chest was symmetrical. There was dullness to percussion in the right base with absent breath sounds. The heart was diffusely enlarged, with distant and poorly heard heart tones, and a prominent protodiastolic third heart sound was present. The abdomen was flat and soft without tenderness. The liver edge was palpable two fingerbreadths below the right costal margin. The spleen was not palpable. The bowel sounds were hyperactive. The extremities were normal except for 2+ edema. There was a blotchy purpuric rash over the lower abdomen. Results of the neurological examination were normal. No lymph nodes were palpable. The genitalia were normal and rectal examination was negative.

Laboratory data. The hemoglobin was 18.5 Gm. per cent, the WBC was 23,000, with 93 per cent neutrophils, 2 per cent lymphocytes, 2 per cent monocytes, 3 per cent band cells, and 1 per cent

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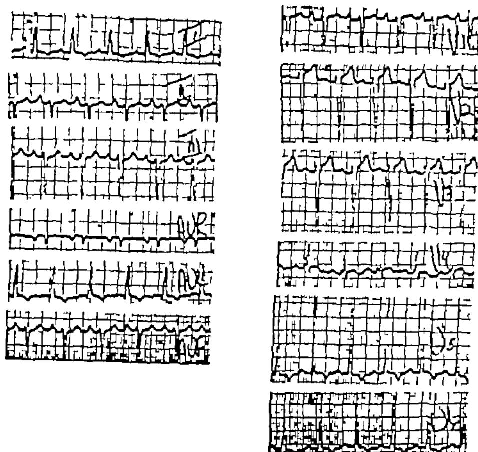


Fig. 1. ECG demonstrated S-T-T changes and probable left ventricular hypertrophy.

metamyelocytes. The platelet count was 39,000. The BUN was 60 mg. per cent and the blood sugar was 130 mg. per cent. The prothrombin time was less than 10 per cent. The serum sodium was 126 mEq. per liter, potassium 7.9 mEq. per liter, chloride 88 mEq. per liter, and CO_2 15 mEq. per liter. The serum calcium was 8.5 mg. per cent and phosphorus was 3 mg. per cent. The uric acid was 15 mg. per cent and cholesterol was 150 mg. per cent. Total protein was 5.6 Gm. per cent with albumin 2.7 Gm. per cent. The serum bilirubin was 8.5 mg. per cent and alkaline phosphatase was 70 mU. per milliliter. The lactic dehydrogenase (LDH) was 3,100 mU. per milliliter, the serum glutamic oxalacetic transaminase (SGOT) was greater than 2,500 mU. per milliliter. The urine was amber, hazy, and acid with a specific gravity of 1.022. There was a trace of proteinuria. Sugar and acetone were negative. The urine was negative for blood but weakly positive for bile. Microscopic examination of the urine sediment was unremarkable. A complete coagulation study revealed a Quick prothrombin time of 38 seconds (10 per cent) and a Duckert prothrombin determination of 40 per cent. Factor V was less than 10 per cent, factor VII 15 per cent, and factor X 30 per cent. Partial thromboplastin time was 161 seconds with a control of 76 seconds. Fibrinogen was less than 50 mg. per cent. A complement fixation test for Rocky Mountain spotted fever was negative as were agglutination for Brucella, Leptospira, and heterophils. ASO titer was 50 units. Cultures of the urine, sputum, and blood were negative.

An ECG on admission revealed S-T-T changes and probable left ventricular hypertrophy (see Fig. 1).

Chest x-ray revealed the heart to have a globular configuration and to be considerably increased in its transverse diameter. The pulmonary vascular pattern was mildly accentuated bilaterally (see Fig. 2).

Course in the hospital. The patient was taken upon admission to the Cardiac Intensive Care Unit, pericardiocentesis was attempted but no pericardial fluid could be obtained. He was given intravenous glucose and insulin because of elevated potassium level and started on Isuprel, heparin, fresh blood, diuretics, digitalis, and prednisone. The blood pressure rose and urinary output increased with Isuprel administration, but the signs and symptoms of severe congestive fail re cont ued without significant improvement. Mild temperature elevation continued.

Despite progressive deterioration in the cardiac status, the ECG showed no significant change. Coagulation studies two weeks after admission showed a Quick prothrombin time of 18 seconds (30 per cent). Duckert prothrombin determination was 55 per cent, factor V 15 per cent, factor VII 45 per cent, and factor X 45 per cent. Partial thromboplastin time was 99 seconds with control of 73 seconds, and the fibrinogen had increased to 205



Fig. 2 Chest roentgenogram showed generalized cardiomegaly with slightly increased pulmonary vascular markings.

mg. per cent. With the improvement in the coagulation studies, a striking decrease in the purpuric rash and in the amount of bleeding with venipuncture was observed. Despite good urine output, the BUN increased progressively to 82 mg. per cent. Electrolytes at this time showed sodium of 121 mEq. per liter, potassium, 4.9 mEq. per liter, chlorides, 84 mEq. per liter, and CO_2 24 mEq. per liter. The total bilirubin increased to 22 mg. per cent, but the serum LDH decreased gradually to 725 mU per milliliter and the SGOT to 400 mU per milliliter. Two days later the patient developed severe hypotension unresponsive to Isuprel and became significantly more obtunded. Following passage of a central venous pressure catheter the patient developed Cheyne-Stokes respirations and weaker heart sounds. External cardiac massage was instituted without success.

Clinical discussion

DR. RICHARD KIRKLAND: The patient, a 25-year-old Negro male schoolteacher, was well until only one month before this final admission. The clinical course was characterized by rapid onset of dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea without chest pain. The absence of chest pain may be of significance. One week following the onset of symptoms he was treated by his physician with penicillin for "bronchitis." Two days later he developed chills and fever and was admitted to the local hospital where his temperature was 100.2° F., pulse 100, respirations 24, blood pressure 100/80. Tonsils were large. His heart was enlarged with regular rhythm.

Lungs showed decreased breath sounds at the right base. The liver was enlarged to two fingerbreadths below the right costal margin.

Chest x-ray showed generalized cardiac enlargement, and the ECG showed left axis deviation. The WBC was increased to 15,200, the hemoglobin was 16 Gm. per cent, the urine was negative. The ASO titer was normal. The BUN was 41 mg. per cent and beta hemolytic streptococci were present in the culture. This organism

may be present in 20 to 30 per cent of normal throats

He was treated with penicillin and digitalis with decreasing fever and increasing heart failure. Acute rheumatic carditis was considered to be present and was treated with steroids. However, after the ASO titer was reported normal, the diagnosis became doubtful. The steroids were stopped and his condition rapidly deteriorated. One wonders if the clinical deterioration might have been due to the withdrawal of steroids or if they may have been administered long enough to produce acute adrenal insufficiency since upon admission to this hospital the serum sodium was low and the serum potassium high. It seems very doubtful, however, that acute adrenal insufficiency would have occurred with such a short course of steroid therapy.

Certain interesting facts which are present in the family history may be of considerable significance. The father is reported to have died of rheumatic heart disease and mitral insufficiency. The mother had a known history of heart disease and the diagnosis of "primary heart disease" had been recently made following cardiac catheterization studies at another hospital. A maternal aunt also had heart disease of unknown type. Are these important facts in the patient's illness or are they simply red herrings? It is frequently difficult to assess the relative importance of family illnesses, particularly when they are not well documented. In addition, the patient drank half a pint of whisky a day during the week and significantly greater amounts on weekends. Since he was quite young, the high alcoholic intake very likely had not been maintained for a long period.

On physical examination the patient demonstrated respiratory distress and cool skin. No blood pressure or palpable pulses were present, and the apical heart rate was 100. He was jaundiced and the neck veins were full. Neck veins might be full in a normal patient if one is lying down and not full if one is sitting up. I will assume, however, that the neck veins were full in a partially upright position. There was no paradoxical filling of the neck veins. Paradoxical filling of neck veins or Kussmaul's sign signifies inflow obstruction to the heart. When one inspires, the neck veins normally empty, but in the presence of heart or lung diseases which obstruct normal venous inflow, the neck veins will increase in fullness on inspiration. Decreased breath sounds and dullness of the right base are compatible with right pleural effusion and consistent with the diagnosis of heart failure. The heart was enlarged. Poor heart sounds and a prominent protodiastolic third heart sound were present. A third heart sound could be normal but when associated with known heart disease is distinctly abnormal. The poor heart sounds and abnormal third heart sound strongly support a diagnosis of intrinsic myocardial disease.

The liver extended two fingerbreadths below the right costal margin and the spleen was not palpable. Extremities showed 2+ pitting edema and a purpuric rash was observed on the abdomen.

The hemoglobin was 18.5 Gm. per cent, which appears somewhat elevated. I cannot explain this. The WBC was 43,000 with 93 per cent polymorphonuclear leukocytes, 2 per cent lymphocytes, 2 per cent monocytes, 3 per cent band cells, and 1 per cent metamyelocytes. Platelets were reduced to 39,000 and the BUN was 60 mg. per cent. The blood sugar was 130 mg. per cent, but the patient was not fasting when it was determined.

The coagulation studies were interesting—the prothrombin time was less than 10 per cent, factors V, VII, and X were decreased, and there was a prolonged partial thromboplastin time of 161 seconds. The fibrinogen was low. I will comment on the coagulation problem a little later. The electrolytes were also interesting—sodium 123 mEq. per liter, potassium 7.9 mEq. per liter, chlorides 88 mEq. per liter, and CO_2 15 mEq. per liter. I believe that the low potassium reading reflects renal failure rather than Addison's disease. The serum sodium may have been low because the congestive failure had been treated with diuretics, but actually the serum sodium in cases of untreated congestive heart failure tends to be on the low rather than the high side of normal. This is interesting in itself, suggesting that increased ADH is a primary factor in

water retention and therefore, may be an important factor in the fluid retention of heart failure In any event, it is not usually this low unless the heart failure has been treated vigorously with diuretics. There were certain disturbing results of liver function studies, and the total protein and albumin fraction were low The bilirubin was 8.5 mg per cent the LDH 3 100 mU per milliliter the SGOT above 2,500 mU per milliliter The liver function findings were strikingly abnormal and worrisome Agglutinations for Rocky Mountain spotted fever Brucella, Leptospira and heterophils were negative. The repeat ASO titer was again normal

The ECG (Fig 1) showed S-T-T changes and possible left ventricular hypertrophy The tracing does not suggest acute myocardial infarction or pericardial disease. It is rather nonspecific and is consistent with left ventricular disease.

The chest x-ray showed an enlarged globular heart with increased pulmonary markings. May we see the x rays, please?

DR. JAMES GLENN All of the films are portable AP chest films. The initial study shows enlargement of the cardiopericardial silhouette both to the left and to the right of the spine probably due to generalized cardiac enlargement. This relatively globular shape also makes it difficult to rule out pericardial fluid radiographically The lungs are essentially clear with minimal pulmonary vascular congestion At the base of the right lung there is a small infiltration. This is most likely due to either pneumonia or pulmonary infarct. Another portable chest film taken on the following day shows an increase in pulmonary vascular congestion Otherwise, there is no interval change One day later there is increased size of the density at the base of the right lung again suggesting either pulmonary infarct or pneumonia. A fourth film was obtained three weeks later During the interval there is little if any change in the appearance of the chest. The density at the base of the right lung is still present, as is the generalized cardiomegaly

DR KIRKLAND I think that the chest x-ray is helpful in showing a lesion at the base of the right lung which is consistent with the clinical diagnosis of pulmonary emboli I was interested in the term "pericardiocardiac shadow" with reference to heart size, which certainly implies neither specific cardiac nor pericardial disease.

The possibility of pericardial fluid was considered and a pericardiocentesis was performed This is an excellent consideration in view of the low blood pressure tachycardia, congestive failure and cardiac configuration on x-ray but no fluid was obtained The patient was treated with glucose and insulin for the elevated potassium with heparin for what was thought to be a consumptive coagulopathy as well as with isoproterenol whole blood diuretics, digitalis, and prednisone The blood pressure and urinary output increased but fever and deterioration in the clinical state continued After hospital admission coagulation studies showed *improvement and* bleeding at the site of venipuncture was significantly decreased The improved coagulation studies could represent a response to heparin perhaps *decreasing the utilization of the bleeding factors or* improving the bleeding tendencies. Progressive azotemia was observed. *The total* bilirubin increased *to a level of 22* mg per cent and this degree of jaundice is particularly bothersome *However* both the LDH and SGOT declined The hypotension became unresponsive to therapy and the patient died.

The clinical course in this case is characterized by rapid onset and progression of cardiac symptoms in a previously clinically *healthy* patient. The rapidity of the myocardial failure suggests an acute process probably involving the muscle wall. Most likely all of the abnormalities present in other organs were the result of myocardial failure. The jaundice, the increased SGOT and the defect in blood coagulation may be attributed to chronic liver congestion with anoxia *as a result of low* cardiac output and heart failure. The SGOT and LDH are extremely high and certainly are considerably higher than usually observed in heart failure but there are no truly satisfactory data *relative* to absolute levels obtained and I will accept these figures as consistent with shock and heart failure. One may observe extremely high levels of these

enzymes with a combination of shock and heart failure. In this case protracted shock could have produced severe liver anoxia and necrosis of liver cells while severe hepatic congestion with heart failure added a further insult.

When patients with a number of serious diseases including protracted shock develop bleeding tendencies and exhibit low coagulation factors one must consider the possibility of disseminated intravascular coagulation. This process leads to fibrinolysis and the formation of split products in the blood while depletion of factors I, V, VII and X results in the overutilization of platelets and abnormal bleeding. This entity termed consumptive coagulopathy occurs in many clinical situations including abruptio placentae, amniotic fluid embolus, sepsis, retained dead fetus, surgical procedures on the lung, open heart surgery, prostatic surgery, carcinoma of the prostate, pancreas, lung or stomach, thrombotic thrombocytopenic purpura and various hemolytic processes. It has also been reported in severe infections, septicemia, cirrhosis, shock, burns and fat embolization. In this case shock played a role in producing consumptive coagulopathy while impaired liver function due to severe anoxia led to inadequate production of the coagulation factors. The kidney failure manifested by declining urinary output and rising BUN was most likely due to low cardiac output and poor perfusion of the kidney. Hypotension, coolness of the extremities, cyanosis and somnolence all represent clinical manifestations in this patient of shock resulting from severe reduction of cardiac output.

The primary problem to be resolved is the etiology of the profound heart failure. No common causes of heart failure appear to be present. There is no history of hypertension. No history of angina or previous myocardial infarction is apparent to make one consider arteriosclerotic heart disease. There have been recent reports of patients, however, who had heart failure in the absence of angina pectoris and myocardial infarction and died suddenly with necropsy evidence of arteriosclerotic disease of the coronary vessels. We cannot make a diagnosis of arteriosclerotic heart disease.

No murmurs were present to make one suspect valvular heart disease. Of course murmurs may disappear in patients with valvular heart disease and markedly decreased cardiac output, but no history is present of heart murmurs or heart disease in earlier life and little evidence is available to support this diagnosis. Cor pulmonale is ruled out by the absence of lung disease and right ventricular hypertrophy.

We must consider causes of heart failure which may involve primarily the myocardium, pericardium, or endocardium. What are the possibilities of pericardial effusion? Viral or tuberculous infections producing pericardial effusion might occur and lead to a marked impairment of heart performance. The pericardiocentesis was negative, however, and I really would not expect a large effusion to be present for a month without being discovered by our clinicians. I do not believe that pericardial effusion on the basis of any infectious process was the cause of the patient's difficulty.

Is constrictive pericarditis a likely diagnosis? The features of heart failure present in this case fit constrictive pericarditis although the heart size is larger than frequently observed with this entity. The loud third heart sound could be due to a pericardial knock. Usually, however, constrictive pericarditis produces a pattern of right-sided heart failure, and pericardial constriction is a longer, more chronic illness than observed in this case. I do not believe constrictive pericardial disease is present.

Insofar as lesions affecting the endocardium are concerned, valvular heart disease, as previously mentioned, may be dismissed because no murmurs are present. Bacterial endocarditis could produce this clinical picture with fever, chills, increased WBC, and congestive heart failure, but multiple blood cultures were negative, which is strong evidence against this diagnosis. It is true that endocarditis arising from the right side of the heart may not yield positive blood cultures in the peripheral veins because the lungs frequently act as a filter to the bacteria. Despite this, however, one can marshall little support for a diagnosis of bacterial endocarditis in this case.

With regard to specific myocardial dis-

ease, one must first consider rheumatic fever. In favor of this diagnosis is evidence of myocardial involvement and previous streptococcal infection. Against it is the absence of other major manifestations of rheumatic fever. Furthermore, the ASO titer was consistently negative and this test is significantly elevated in 80 per cent or more of the cases of rheumatic fever. An initial attack or even recurrence of rheumatic fever would be rare at the age of 25.

Vasculitis involving the myocardium such as might occur in polyarteritis is a consideration. This entity could lead to multiple organ infarcts and possibly produce failure in multiple peripheral organs. Furthermore, heart failure occurs in over half and congestive failure in at least 40 per cent of patients with polyarteritis.

The patient had neither eosinophilia nor previous history to suggest a drug allergy except for recent penicillin therapy. The penicillin, however, was given after the onset of heart failure. There is little to support the diagnosis of polyarteritis. Other collagen diseases, such as thrombotic thrombocytopenic purpura and lupus, could cause much of this picture. We have no evidence for hemolytic anemia or helmet cells on the peripheral blood smear, both of which are consistent with this diagnosis. Lupus may cause arteritis of the heart, but no LE cells were reported.

A number of systemic diseases, including amyloidosis, scleroderma, and sarcoidosis, are known to involve the myocardium and produce marked deterioration in cardiac performance. There is little or no evidence, however, for these clinical entities, and I will dismiss them as likely possibilities in this case. Sarcoidosis might be considered more strongly since the patient resided in an area with a rather high incidence of the disease and was of the Negro race. There is, however, no evidence such as lymphadenopathy or abnormal pulmonary findings to support such a diagnosis, and most frequently the myocardial dysfunction presents as cor pulmonale.

I believe that the diagnosis in this case falls within the general category of intrinsic myocardial disease. The term implies that the etiologic agent affects heart muscle directly and may produce severe cardiac dysfunction. It explicitly fails to recognize a single etiologic agent as the causative factor in a specific clinical situation. Could this be acute myocarditis, possibly due to an infectious agent or toxin? Certainly the clinical course is consistent with the diagnosis. The sudden and rapid onset of cardiac deterioration in a previously asymptomatic person as well as the physical findings of poor heart sounds and gallop rhythm are typical of a fulminating myocarditis. The ECG is worrisome, however, because in this case it shows a fairly stable pattern of left ventricular preponderance, whereas in acute myocarditis changing patterns associated with conduction defects, low voltage, and S-T–T shifts are most frequently observed. The electrocardiographic changes do not support a diagnosis of an acute myocardial process but rather of a more chronic myocardial disease.

The chronicity of the process, at least on the basis of the ECG findings, might suggest a cardiomyopathy or myocardosis. Of course, this latter diagnosis could represent the end stage of acute myocarditis. This disease has a predilection for Negroes and males, but the clinical course is typically slower in onset and progression than acute myocarditis. The physical findings could closely mimic those observed in acute myocarditis.

Numerous etiologies have been suggested as causes of cardiomyopathy, including autoimmunity, alcohol, toxins, thiamine deficiency, the the postpartum state. The entire chronic process termed cardiomyopathy may actually represent the end stage of many nonspecific insults to the myocardium.

A last intriguing possibility is so-called familial cardiomyopathy. This disease has been considered to be genetically related. The family history is certainly consistent with the diagnosis, although clear documentation of cardiomyopathy in the relatives has not been made. The patients thus far reported as under the heading of familial cardiomyopathy do not represent a distinct and homogeneous group from the pathophysiological standpoint, but many with cardiac failure and severe cardiac dilatation

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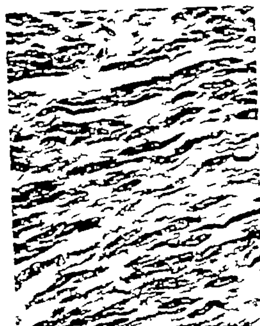


Fig. 5 Photomicrograph of representative region of left ventricular myocardium showing extensive diffuse interstitial fibrosis, moderately trophic but regularly oriented muscle fibers, and absence of any inflammatory infiltrate. (Hematoxylin and eosin ×100.)

the ventricular wall was also demonstrated histologically

Numerous sections of the myocardium of all chambers exhibited a rather uniform general appearance with areas of collagen deposition intervening between the muscular bundles (Fig 5) The muscular bundles showed an average increase in size but with considerable variation between cells particularly in the interventricular septum where the fibers showed considerable atrophy and shrinkage from the perimysial sheath

Throughout the myocardium a strikingly similar type of histological change was observed consisting of focal deposits of collagen as well as a diffuse increase in collagen infiltrating between muscle bundles. Special stains confirmed the presence of increased amounts of fibrous or collagen tissue. One noteworthy feature present was the virtual absence of any disorderly array of muscle bundles, a finding usually present in idiopathic cardiomyopathy Classically in this latter entity the muscle bundles not only are enlarged and of variable size, but also are distributed in bizarre architectural form with coiled and twisted cells displayed in a random fashion. The absence of inflammatory cells or rheumatic stigmas lent no support to the diagnosis of infectious or rheumatic myocarditis.

This case represents idiopathic cardiomyopathy from the pathological standpoint The heart is enlarged and diffusely and extensively replaced by fibrous tissue What might be considered the most likely causes of this lesion? They have been well reviewed by Dr Kirkland One additional point, however with reference to the family history should be made. We now know—and this information was not supplied to Dr Kirkland—not only that two aunts were affected by heart disease at an early age but also that the patient's mother died of primary myocardial disease in her late forties several months after this patient's death. In addition the maternal grandmother died in early life with heart disease.

Three possibilities exist, therefore to explain the cardiomyopathy (1) A strong family history of heart disease suggests a familial basis (2) a febrile illness prior to the initial onset of cardiac signs and symptoms suggests a possible infection as the cause of the cardiac disease and (3) an excessive alcoholic intake might be inferred as a cause of the patient's illness.

The pathological findings are compatible with any of these causative effects. The specific etiology of cardiomyopathy depends upon the details of the clinical history I would agree with Dr Kirkland that the majority of cases of alcoholic cardiomyopathy are observed in older patients who usually have longer histories of excessive alcoholic intake. Viral and bacterial cultures taken from the heart, kidney and lungs at postmortem examination were negative but do not completely rule out an infectious origin and cardiomyopathy as seen in this case may evolve from an earlier acute myocarditis. The family history is most intriguing and one certainly cannot rule out a familial relationship

ANATOMICAL DIAGNOSIS *Cardiomyopathy idiopathic ? familial.*

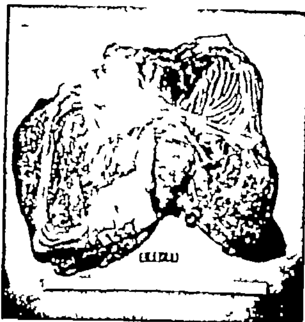


Fig 3 Right side of heart at autopsy showing dilatation and hypertrophy of ventricle and atrium with large mural thrombus in right atrium



Fig 4 Left side of heart showing left ventricular dilatation and hypertrophy normal mitral valve and dilated left atrium with somewhat opacified but not thickened endocardium

have been reported They are from a clinical standpoint indistinguishable from those with cardiomyopathy or chronic myocarditis

In summary I believe that the case today represents acute myocarditis probably due to a virus The ECG is worrisome in relation to this diagnosis but the clinical course is quite consistent The possibility however of familial cardiomyopathy is a strong second choice

CLINICAL DIAGNOSIS *Acute myocarditis viral?*

DR MOON The pathological discussion of today s case will be presented by Dr Shiel

Pathological discussion

DR SHIEL I will discuss the incidental findings and then proceed to the pathological findings in the heart. The lungs were moderately edematous weighed 1 600 grams and showed focal edema and infiltration of a moderate number of polymorphonuclear leukocytes. The pulmonary vessels were carefully searched and no thrombi were found In the lower lobe a small infarct was found but this was not associated with any demonstrable thrombus or embolus.

The liver exhibited gross chronic venous congestion and severe centrilobular fatty degenerative change

The pancreas showed a mild degree of focal fat necrosis As there was no mention of pancreatitis in the clinical history I presume that this was a terminal event.

The heart was enlarged and weighed 500 grams The right ventricle and right atrium were moderately hypertrophied and dilated (Fig 3) and a mural thrombus was present within this latter chamber The left side of the heart (Fig 4) also demonstrated the presence of a few mural thrombi but there was no evidence of endocardial disease and in particular no suggestion of endocardial fibroelastosis. The left atrial endocardium however was slightly opaque although not notably thickened Gross inspection of the mitral valve excluded the possibility of overt rheumatic carditis. The cusps were not shrunken the chordae tendineae appeared immaculate and the only minor abnormality observed in the cusps was a slight increase in opacity probably consistent with the patient s age. Examination of a section of the left atrium confirmed the macroscopic impression The endocardium was slightly thickened with no evidence of elastosis. A mural thrombus adhering to



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ANATOMICAL DIAGNOSIS: *Cardiomyopathy idiopathic ? familial*

DR. MOON: Are there any questions?

DR. JAMES: Were the staining characteristics of the heart muscle itself normal?

DR. SHIEL: Yes, apart from the fact that there were moderately severe autolytic changes, the surviving cells showed no tinctorial abnormality.

DR. JAMES: And did you do electron microscopic studies?

DR. SHIEL: No. Autopsy was not performed until several hours after death, and autolytic changes were already prominent.

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Fundamentals of clinical cardiology

The role of magnesium in digitalis toxicity

Robert H. Seller, M.D.
Philadelphia, Pa.

The effect of magnesium on the cardiovascular system has been studied since 1900.[1] Knowledge of magnesium metabolism was difficult to obtain because of the lack of a simple and precise method for measuring magnesium concentrations in biological material. With improved analytic methods for measuring magnesium, especially atomic absorption spectroscopy, knowledge of the biological role of magnesium has increased. Despite the low concentration of magnesium in the extracellular fluid, where one third to one half is protein bound, magnesium is second only to potassium in intracellular concentration.[2] Magnesium is a metallocoenzyme for many enzymatic reactions of carbohydrate and protein metabolism. It is also a metallocoenzyme in reactions involving oxidative phosphorylation and activates adenosine triphosphatase (ATPase) which is essential for normal cell membrane function. It is intimately related to the electrophysiology of conduction in myocardial tissue.

Most investigations concerning the relationship of electrolytes to the toxic manifestations of digitalis have concerned themselves primarily with potassium and calcium.[3] These studies have shown that potassium salts protect the myocardium from digitalis toxicity (possibly by influencing myocardial glycoside binding) and that conversely digitalis protects against the toxic manifestations of hyperkalemia. It is well recognized that potassium depletion sensitizes the myocardium to the development of digitalis toxicity.[7] Studies of the role of calcium in myocardial function have shown that this ion increases myocardial contractility and excitability. Calcium may also potentiate the development of digitalis toxicity. Thus calcium chelating agents have been recommended for the treatment of digitalis toxicity but their therapeutic benefits are often transient.

The primary cardiovascular effects of magnesium involve myocardial conduction and contraction as well as blood pressure regulation.[4] The intravenous administration of magnesium sulfate causes a prolongation of the P-R interval as serum magnesium concentration increases. With continued administration there is a prolonged intraventricular conduction. In general, the electrocardiographic manifestations of hypermagnesemia are similar to those of hyperkalemia, while the changes of hypomagnesemia are similar to those of hypokalemia. Some investigators feel that magnesium depresses the conduction and the spontaneous rhythm of the heart. They suggest that one of the mechanisms underlying these effects may be an accumulation of intracellular potassium as a result of a magnesium-induced reduction in membrane permeability to potassium out-

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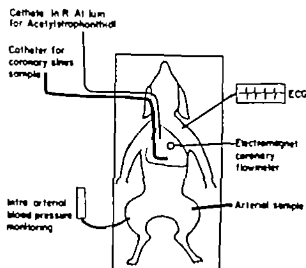


Fig 3 Schematic representation of animal experiments.

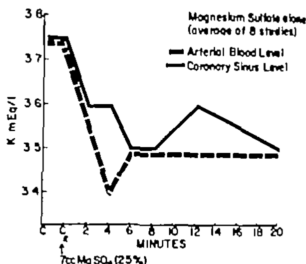


Fig 4 The effect of magnesium sulfate alone on transmyocardial potassium kinetics. Serial determination of magnesium levels in arterial and coronary sinus serum taken after 7 ml of 25 per cent magnesium sulfate was injected into the right atrium. It is notable that the administration of magnesium sulfate caused a prompt drop in arterial potassium concentrations of 0 34 ± 0 17 mEq per liter suggesting an intracellular shift of potassium

with an electromagnetic flowmeter Intra arterial blood pressure was monitored with a Statham strain gauge Acetylstrophanthidin and or magnesium sulfate was injected through a catheter placed in the right atrium Another catheter was placed in the coronary sinus under fluoroscopic guidance Simultaneous blood samples were taken from the coronary *sinus (CS) and* femoral artery (FA) at two-minute intervals (Fig 3)

The effect of magnesium sulfate alone on transmyocardial potassium kinetics was studied in eight dogs 7 ml of 25 per cent magnesium sulfate was injected into the right atrium and samples were obtained simultaneously from the coronary sinus and femoral artery The administration of magnesium sulfate caused a prompt drop in arterial potassium concentration of 0 34 ± 0 17 mEq per liter ($p < 0\ 05$) suggesting an intracellular shift of potassium (Fig 4) No significant changes were noted in the transmyocardial potassium gradient (CS-FA) nor were any significant changes noted in sodium calcium or pH There was a transient drop in blood pressure which returned to normal within two minutes of administration of magnesium sulfate

The effects of acetylstrophanthidin alone and the combination of acetylstrophanthidin and magnesium sulfate on myocardial potassium kinetics were studied in a similar fashion in 16 dogs. Serial injections of acetylstrophanthidin were performed at 2½ hour intervals During the last acetylstrophanthidin injection magnesium sulfate *(25 per cent)* was given *simultaneously* with the acetylstrophanthidin After the first acetylstrophanthidin infusion the maximal difference in potassium concentration (CS-FA) occurred between 2 and 8 minutes and averaged 0 47 mEq per liter In six studies when the second dose of acetylstrophanthidin was repeated 2½ hours after the first there was a significantly greater potassium egress (0 80 mEq per liter) than after the first dose When magnesium sulfate was given simultaneously with acetylstrophanthidin infusion there was no significant egress of myocardial potassium (Fig 5)

The difficulty in interpreting these studies arises because of the inconsistent relationship of myocardial potassium egress to arrhythmia Although myocardial potassium egress usually occurred *after the* administration of acetylstrophanthidin alone it did not always result in the development of an arrhythmia After the first acetylstrophanthidin infusion *all arrhythmias* but one were associated with potassium egress. One third (5 out of 15) had no arrhythmias and no statistically significant

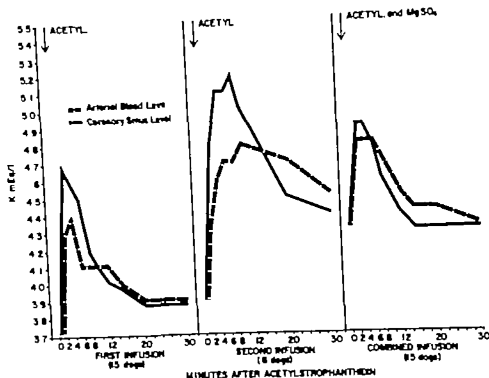


Fig. 5 The effect of acetylstrophanthidi alone nd the combination of acetylstrophanthidi and magnesium sulfate on the myocardial potassium kinetics. The graph demonstrates mean serum potassium levels in simultaneous samples of arterial and coronary blood after serial infusions (1½ hours part) of 1 mg. of acetylstrophanthidin (and 7 .c. of magnesium sulfate) The first infusion resulted in maximal difference in potassium concentration of 0 47 mEq. per liter After the second dose of acetylstropha thidin, there was greater potassium egress as demonstrated by difference between coronary sinus and arterial samples of 0 80 mEq. per liter When magnesium sulfate was given simultaneously no significa t egress of potassium was noted.

potassium egress. It is notable that in all six studies, where acetylstrophanthidin alone was administered a second time, arrhythmias occurred and potassium egress was marked. Most importantly although the coadministration of magnesium sulfate blocked potassium egress in 100 per cent (15 out of 15) arrhythmias still occurred in nine animals. In other words, despite the fact that magnesium sulfate consistently blocked the egress of myocardial potassium in all studies arrhythmias occurred in 60 per cent of the animals. Our results imply that factors other than myocardial potassium egress were responsible for these digitalis-induced arrhythmias.

Discussion

In the past magnesium sulfate has been used in the treatment of digitalis arrhythmias without regard to serum magnesium levels. We have demonstrated that hypomagnesemia facilitates digitalis toxicity and that in these instances magnesium sulfate is able to abolish the arrhythmias promptly and permanently This is particularly important in view of the fact that many clinical conditions have been reported to be associated with hypomagnesemia They include prolonged magnesium free intravenous fluid administration diarrhea diabetes mell tus, congestive heart failure cardiopulmonary bypass, prolonged gastrointestinal drainage, acute pancreatitis, delirium tremens, alcoholic cirrhosis, malabsorption hyperparathyroidism aldosteronism excessive lactate administration thyrotoxicosis, malignant osteolytic disease (hypercalcemia and hypomagnesemia) and *particularly d uretic therapy*

Rather than the empiric use of magnesium sulfate as an antiarrhythmic agent we believe that t is important to determine both serum magnesium and potassium in

all cases of digitalis toxicity. If hypomagnesemia is present, we recommend that 7 to 15 c.c. of 25 per cent magnesium sulfate be administered slowly intravenously under electrocardiographic monitoring.

Although several investigators believe that the loss of myocardial potassium underlies the development of digitalis arrhythmias, other investigators have suggested that myocardial potassium egress is but one of the factors leading to digitalis arrhythmias.[16,17] The fact that several antiarrhythmic agents, including quinidine sulfate, diphenylhydantoin, procaine amide, glucose and insulin, as well as magnesium sulfate, all reduce the digitalis-induced myocardial loss of potassium and suppress the arrhythmia suggests that egress of potassium underlies the genesis of some digitalis arrhythmias. On the other hand, propranolol and reserpine, also useful in digitalis arrhythmias, do not affect myocardial potassium kinetics. This suggests *that factors in addition to myocardial* potassium egress play a role in the genesis of some digitalis arrhythmias. Our studies demonstrated that magnesium sulfate shares with other antiarrhythmic agents the ability to reduce the loss of myocardial potassium induced by digitalis. The latter property may explain magnesium's antiarrhythmic activity. Since the magnesium ion is a coenzyme for membrane ATPase which is inhibited by digitalis glycosides, it is interesting to speculate that the presence of magnesium in excess may, to some degree, overcome digitalis blockade of this enzyme.

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Appraisal and reappraisal of cardiac therapy

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Management of patients with pheochromocytoma

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Because of striking advances during the past 15 years in our knowledge of human catecholamine metabolism [1] diagnostic capabilities for pheochromocytoma are far more promising than they are for most neoplasms. A tumor benign in its histologic behavior in over 90 per cent of the cases, pheochromocytoma is nevertheless almost uniformly lethal if unappreciated and therefore untreated. Grievous inadequacy in premortem detection of these lesions was perhaps best explained by the proclivity for these rare tumors to elicit a clinical picture indistinguishable from various common illnesses. [2]

Diagnosis

No more than a few tenths of 1 per cent of the 20 million hypertensive subjects in the United States harbor a pheochromocytoma, but clinical acumen alone will fail in the majority of instances to separate the proverbial needle from the haystack. Rather the diagnosis of pheochromocytoma has become one in which the clinician is almost totally dependent upon the laboratory the physician's major diagnostic function being that of demanding that valid biochemical assay procedures[3] be used for screening the appropriate patients (Table 1) Too often the clinician assumes that the clinical laboratories use only those biochemical techniques that offer specificity and reliability Since pheochromocytomas occasionally result in only minimal derangements in catecholamine synthesis, the failure of the clinical laboratories to use valid assay procedures becomes especially critical Vanillylmandelic acid (VMA) and total metanephrines (metanephrine + normetanephrine) are currently the catecholamine metabolites commonly assayed for diagnostic purposes (Fig 1)

The most widely used screening procedures for detection of pheochromocytoma are the spectrophotometric assays for VMA techniques repeatedly criticized for their lack of either specificity or reliability Most of these techniques necessitate the collection of 24 hour urine specimens, a feat requiring for some odd reason greater abilities and aptitudes than those possessed by most patients and paramedical personnel.[10,11] Fortunately the physician can suspect that an inadequate assay procedure has been used for measurement of VMA excretion whenever it is expressed as "mg per 24 hours. The excretion of VMA by normal subjects (studied with the benefit

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Table I. Patient symptomatology or history requiring biochemical screening for pheochromocytoma

Variables	Physician action
Hypertension (sustained or labile) Paroxysmal symptoms Hypermetabolic states Pressor or depressor response to mild trauma, anesthesia, or parturition Consanguinity with a patient having a pheochromocytoma Neurocutaneous syndromes (von Hippel-Lindau or von Recklinghausen's) Type II multiple endocrine neoplasia	Patient presenting with one or more of these variables should undergo valid biochemical testing for pheochromocytoma

of bidirectional paper or gas liquid chromatographic methods) varies from 0.70 to 3.5 *μg per milligram creatinine. These pro*cedures require no more than a random urine specimen and differ from the spectrophotometric techniques in that they are not influenced by diet or by the majority of commonly used drugs. Reliable VMA assays yield diagnostic accuracy in 96 per cent of patients with pheochromocytoma. *In the absence of coma or a tumor of neural* crest origin, VMA excretion in excess of 5 μg per milligram creatinine will rarely, if ever, be found.

A reliable photometric method for measurement of total metanephrines (TM)[7,8] although readily available, may be used less frequently than it deserves because *of* the clinical laboratory's *disinclination to* employ column chromatographic and/or photometric techniques. At this laboratory the excretion of 2.2 μg TM per milligram creatinine was exceeded by each of the 107 subjects who were surgically proved to harbor a pheochromocytoma. Unfortunately, the severe stress associated with shock, congestive heart *failure, overwhelming sepsis,* respiratory insufficiency, and widely disseminated metastatic neoplasia may result in the elevation of TM excretion. *These* false-positive results are uncommon and can be subjected to further critical evaluation by synchronous measurement of VMA excretion, which is almost always normal.

In rare instances (3 per cent of cases with pheochromocytoma) patients may excrete 2.2 to 4.5 μg of TM per milligram creatinine and 3.5 to 5.0 μg of VMA per milligram creatinine and pose a diagnostic problem for the physician. Under these unusual circumstances one might turn to the use of the various pharmacologic tests[4,12,13] or assays of the unchanged catecholamines in plasma *or urine.*[4] *The pharmacologic studies* pose a hazard to these patients and frequently yield misleading information. Similarly, catecholamine assays may be difficult to interpret because of technical problems inherent in their measurement and sample *collection, as well as in the* variability of tumor secretion and in the frequency with which drug administration interferes with their determination.

In summary, abnormally elevated excretion of VMA and TM when assayed by reliable techniques in two urine samples *from a conscious patient is sufficient to* make the presumptive diagnosis of a neural crest lesion. It has been the experience at this laboratory that other biochemical measurements as well as pharmacologic testing fail to offer significant assistance in the correct evaluation of those rare patients who excrete quantities of both TM and VMA *within a borderline or indeterminate* range. Tumors secreting predominantly or solely epinephrine (E) seem to fall within this category somewhat frequently, and under such circumstances the separate determination of (1) metanephrine (M) as opposed to normetanephrine (NM) or (2) of epinephrine (E) as opposed to norepinephrine (NE) might offer diagnostic insight.

In rare instances, the combination of clinical suspicion and borderline elevations of catecholamine catabolite excretion necessitates roentgenographic efforts aimed at a demonstration of a tumor in a location compatible with the diagnosis of pheochromocytoma.[14-17] A more successful technique for dealing with this bewildering problem is that of continued observation of the *patient over a period of months during* which time he may be adequately protected by administration of an adrenolytic drug

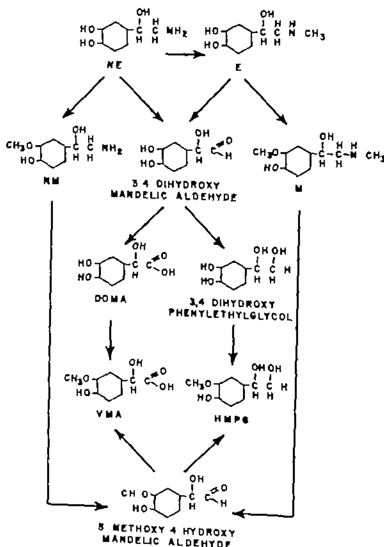


Fig. 1. Catabolic pathways of norepinephrine and epinephrine. *NE*, norepinephrine; *E*, epinephrine; *NM*, normetanephrine; *M*, metanephrine; *DOMA*, 3,4-dihydroxymandelic acid; *VMA*, vanillylmandelic acid; *HMPG*, 3-methoxy-4-hydroxy-phenylethyleneglycol.

Periodic catecholamine catabolite determinations have thus far sufficed to detect the majority of patients with pheochromocytoma who fall within this category.

The observation of abnormally elevated homovanillic acid (HVA) excretion in an adult indicates the presence of a malignant neural crest lesion.[illegible] On the other hand, normal HVA excretion fails to rule out malignancy since the majority of such lesions are not associated with elevated excretion of this dopamine catabolite. In childhood, a benign pheochromocytoma can be associated with abnormally elevated HVA excretion negating the use of HVA assay for biochemical differentiation of malignant from benign neural crest lesions in pediatric patients.[illegible] The infrequency of neuroblastoma and ganglioneuroma above the age of adolescence simplifies interpretation of elevated catecholamine catabolite excretion. Although neuroblastoma is most frequently associated with grossly elevated VMA, 3-methoxy-4-hydroxyphenylethyleneglycol (HMPG), and HVA excretion whereas pheochromocytoma usually reveals modestly elevated VMA and more notably elevated TM excretion,[illegible] such biochemical

patterns as well as the presence or absence of hypertension fail to adequately differentiate these neural crest lesions during childhood. At times nothing short of surgical resection offers a definitive diagnosis, and occasionally tumors with various mixtures of neuroblastoma, ganglioneuroma, and pheochromocytoma may be found.[22,23]

Preoperative management

Having attained biochemical certainty of the presence of a neural crest lesion and from the age and clinical appearance of the patient deduced a pheochromocytoma as most likely, how should one proceed? Although there have been sporadic reports of individual patients refusing surgery or presenting with other medical problems of such gravity as to preclude resection of tumor,[24,25] the overwhelming need for removal of this neoplasm or at least for an accurate tissue diagnosis (in the case of a child) demanded surgical intervention in each one of the 107 patients studied at this laboratory. Interestingly, age proved no barrier to such management. One patient with malignant hypertension, rapidly progressive blindness (Grade IV retinopathy), cardiac enlargement, and left bundle branch block was 72 years old at the time of his diagnosis. His surgical course was uneventful and postoperatively he recovered both his normal blood pressure and his eyesight. The presence of a complicating metastatic neoplasm or of pregnancy may dissuade one from early surgical intervention. In the latter instance, the physician is faced with the dilemma of early tumor resection almost invariably resulting in fetal loss versus delayed surgery with its incumbent hazard to both mother and infant.[26,27] The relative safety of long term administration of adrenolytic compounds for the fetus, vaginal delivery in association with adequate α and β receptor blockade, or elective cesarean section with simultaneous tumor resection late in the third trimester cannot be definitively evaluated at this time.

In the patient for whom no contraindication to surgery exists, the major rule for preoperative management is that he should undergo no unnecessary tests or manipulations. Circumstances appearing to be most innocuous have been associated with sudden death in these subjects. The corollary to this rule is that all deliberate haste be exercised in preparing the patient for tumor removal. Should a considerable delay be absolutely unavoidable, the use of adequate quantities of adrenolytic drugs is mandatory. Such therapy would differ minimally from the definitive care given to a patient with a malignant or otherwise unresectable pheochromocytoma.[28] The drug of choice in such instances is phenoxybenzamine administered orally at least twice daily in 10 mg capsules, the total daily dosage often exceeding 150 mg. One should attain elimination of paroxysms, hypertension, sweating, weakness, progressive weight loss, and the other commonly noted signs and symptoms associated with this tumor. Administration of a few capsules per day will rarely effect a degree of α blockade sufficient to guarantee complete safety, although disappearance of prominent symptomatology occasionally deludes the observer into a false sense of security. Combinations of certain adrenolytic agents may actually interfere with the achievement of this result. Although considerable attention has been directed toward the use of β blocking drugs such as propranolol for these patients, the unequivocal need for β blockade above and beyond adequate α blockade has been only rarely noted.[29,30] Moreover, adequate α blockade must be achieved prior to administration of a β blocking agent or severe hypertensive episodes might result.[31] We have not been impressed with the need for β blocking agents in the patients so far observed. Phenoxybenzamine may cause gastrointestinal distress, nasal stuffiness, and excessive sedation, but it is generally well tolerated by these subjects. Postural hypotension may not be diminished during such therapy.

The use of α methyl p-tyrosine to block synthesis of the catecholamines has more recently been advocated in the chronic medicinal management of pheochromocytoma.[32,33] Prepared as 250 mg capsules, it is unusual for less than 2 capsules to exert any visible effect upon the patient's clinical status. The excretion of catecholamine catabolites usually falls upon the daily admin

istration of 1.5 to 3 Gm. of this drug. However, even modest dosage may lead to a clinical syndrome bearing a striking resemblance to Parkinsonism, including its partial relief by administration of diphenhydramine.[36] Although there have been individual case reports wherein α-methyl-p-tyrosine succeeded but phenoxybenzamine failed to control the hyperadrenergic state associated with pheochromocytoma,[22] the latter drug remains the most reliable and least toxic agent for the majority of patients. The action of phentolamine is too brief and its effect when given by mouth too variable for such long term use.

Although rare instances in which malignant pheochromocytomas have responded to radiotherapy have been reported, both this modality as well as cytotoxic agents generally fail to induce beneficial response. Malignant pheochromocytomas may be slow growing and therefore occasional survival beyond five years is not unusual, especially during control of the metabolic effects of the tumor with appropriate adrenolytic drugs.[1,23] On the other hand, over one half of such patients die within two years of their diagnosis despite this type of management. Metastasis by contiguity is most often noted, but widespread hematogenous dissemination may also be observed. Definitive surgical resection of malignant pheochromocytoma is rarely possible.

Interim medicinal management is occasionally required for patients harboring multiple pheochromocytomas, some of which have previously been resected. Such instances are most frequently noted in childhood and represent the major and perhaps singular indication of attempts to localize neural crest lesions within the abdomen. One such child had five benign pheochromocytomas removed from the abdomen at initial surgery, a sixth lesion removed from the thorax one year later, and presented some years afterward with biochemical and clinical evidence of at least one additional neural crest tumor somewhere in the abdomen. While awaiting either tumor growth or adequate localization, this patient has remained asymptomatic under treatment with adrenolytic agents. Because of the technical difficulties associated with re-exploration of the abdomen in such a patient, two techniques may occasionally be used for tumor localization: selective venous sampling for catecholamine assays and selective angiography. In both instances, the patient with a pheochromocytoma is exposed to a degree of manipulation entailing significant risk, and detailed arrangements must be made for administration of adequate adrenolytic medication should the need arise. All too often the latter is accomplished by administration of a bolus of phentolamine. The occasional episode of irreversible shock which follows such treatment may be avoided by having the patient prepared for blood pressure monitoring and administration of phentolamine or norepinephrine intravenously in a manner similar to that used during administration of anesthetics for surgery. At all times one must be adequately prepared to titrate such patients rather than react to their violent changes in vital signs by equally violent administration of medicinal agents. Whether related to problems inherent in the fluorimetric assay of plasma catecholamines or to paroxysmal fluctuations in the release of these substances by the tumor, we have experienced less success in tumor localization by selective venous catecholamine assays than that occasionally noted by other investigators.[36-37] Similarly, efforts aimed at angiographic localization[17] of these tumors (selective venography or arteriography) have yielded false-positive or false-negative results often enough to seriously compromise the clinical usefulness of such studies. The inadequacy of the techniques available for tumor localization, so unfortunate for patients requiring repeat abdominal explorations for resection of additional tumors, is of little concern for the majority of patients who are about to undergo their initial surgical procedure. In the latter group about 15 per cent of adults and 40 per cent of children will have more than one tumor when the patient is first treated. Under these circumstances the use of an occasionally inaccurate but potentially harmful testing procedure appears quite invalid and nothing short of an adequate anterior abdominal surgical exploration will fulfill the requirements for total tumor resection. Fortunately, over 98 per cent of these lesions are within the

abdomen, the majority of the rest being not only located within the chest but almost always visible upon careful roentgenographic evaluation. This must include posteroanterior, lateral, and both anterior oblique views of the chest and, should doubt remain, tomography as well. Despite reports to the contrary,[9,35] this laboratory and at least one other[4] have studied patients in whom the relative excretion of E as opposed to NE or of M as opposed to NM failed to correlate with the location of their pheochromocytoma.

Retroperitoneal insufflation, a procedure advocated some years ago for localization of pheochromocytomas,[16] must be eschewed because of its inherent inaccuracy as well as on account of the occasional hazard associated with its use.[4] If not specifically contraindicated, an intravenous pyelogram should be routinely obtained, not for purposes of tumor localization but rather to demonstrate the presence of bilaterally functioning kidneys prior to the occasional necessity to sacrifice a kidney whose vascular supply is discovered in the operating room to be inseparably related to the tumor. A surprisingly high incidence of cholelithiasis[7,39] could not be confirmed in this series and therefore routine cholecystography cannot be advocated. Even if coexistent gallbladder disease were detected prior to or during surgery, it would be inadvisable to extend the surgery into the biliary system and convert a clean operation to a contaminating procedure. Since pheochromocytoma is a life-threatening disease, it should never be preceded by or combined with any form of elective surgery for chronic disease elsewhere. The morbidity and mortality rates from such ventures are prohibitive.

Persistent hypotension requiring the administration of pressor agents following resection of a pheochromocytoma has been ascribed to an intrinsic deficiency in blood volume noted in some of these patients prior to surgery.[40] Advocates of preoperative blood transfusions have been forced to reconsider this therapeutic approach in light of the observation that such blood volume disturbances occur in no more than a small minority of such patients.[7] It would appear that this postoperative difficulty more likely arises from the sudden disproportion between vascular capacitance and blood volume which must follow the acute diminution in circulating catecholamines immediately following tumor resection. A successful although empiric method of handling this circumstance is that of adequate preoperative α-blockade in conjunction with the initiation of blood or other intravascular volume expanders at the moment of commencing surgery. In our experience, the need for routine administration of corticosteroids, advocated by some observers,[9] could not be confirmed. The administration of an adrenolytic compound for a minimum of 12 hours prior to surgery will usually fulfill the above requirements, and whether oral or parenteral phenoxybenzamine or parenteral phentolamine is used for this purpose matters little. The long action of phenoxybenzamine, an advantage in the definitive or ambulatory management of a patient with an unresectable pheochromocytoma, becomes a disadvantage in the critical moment-to-moment management of the patient immediately prior to and during tumor resection. The evanescent action of intravenously administered phentolamine has been found preferable in our hands, but one must caution that this drug be administered by titration rather than by bolus injection. One must be prepared to utilize whatever amounts of phentolamine (2 to 50 mg. per hour) may be required in order to lower the blood pressure while maintaining parenteral volume administration within reasonable limits. Under these circumstances one should hesitate to undertake such preoperative preparation with less than many dozens of the 5 mg. phentolamine ampules on hand or readily available. The use of phentolamine in the above manner has not resulted in such a degree of adrenergic receptor blockade as to obscure the clinical cardiovascular signs of tumor localization and removal used by the surgeon during his operative procedure. These advantages may be lost, however, if the patient is given doses of α-methyl-p-tyrosine adequate to markedly inhibit catecholamine synthesis. Neither the clinical experience of this group nor recent publications[31-33] dealing with the use of β-blocking drugs have convincingly

documented the routine need for these substances in the preoperative management of patients with neural crest lesions.

In preparation for removal of abdominal pheochromocytomas, the use of colonic enemas should be avoided since crises may be induced with this method of cleansing the colon. The use of oral cathartics and restriction to fluid diet for 24 to 48 hours prior to surgery is a reasonable alternative. Such preparation of the large bowel is necessary because of the operative manipulation of the hepatic and splenic flexures of the colon in the process of exposing the adrenal glands.

The use of a narcotic analgesic in conjunction with scopolamine has been favored for preanesthetic medication.[31] Atropine, occasionally followed by tachycardia,[42] and phenothiazines which may cause severe hypotension[8] are usually avoided.

Surgery

In the operating room, cardiac activity as well as arterial and central venous pressures are monitored continuously by means of appropriately placed catheters. A separate venous line is used for infusion of drugs: phentolamine and norepinephrine are prepared in two different concentrations for immediate infusion when needed. The same strength phentolamine solution used preoperatively and a fivefold concentrated solution are necessary, while the dilute (8 µg per milliliter) and concentrated (64 µg per milliliter) solutions of norepinephrine are reserved for hypotensive crises, particularly following resection of the tumor. The interconnections of the intravenous tubes should be so arranged as to permit a change in administration from one drug solution to another without significant time lag.

Human albumin is adequate as a substitute for whole blood, if the blood loss is not excessive. The infusion of albumin begins with the skin incision and is maximized immediately after ligation of the major venous outflow from the tumor, thus avoiding the need for vasopressor drug support. A total of 50 to 75 Gm. of albumin is usually necessary.

The induction of anesthesia and endotracheal intubation are performed under adequate α-receptor blockade. During induction, thiamylal is given continuously but slowly in order to prevent a hypotensive response. Endotracheal intubation is carried out only after the level of surgical anesthesia has been attained by breathing halothane or other anesthetic, with curare used preferentially as a muscle relaxant. The choice of the anesthetic itself varies widely and no particular agent is safe or hazardous. Maintaining proper oxygen and CO_2 levels will go far to prevent serious arrhythmias. The old concept that halogenated anesthetics are risky because of their arrhythmogenic properties in the presence of excess circulating catecholamines[43] has not been substantiated in clinical practice. In fact, hypertensive crises coupled with arrhythmias that are difficult to control with phentolamine and antiarrhythmic drugs have been managed by increasing the depth of anesthesia with halothane. The compatibility of halothane anesthesia with combined β-adrenergic and cholinergic blockades in patients with normal cardiovascular and respiratory systems has been demonstrated.[44] Most frequently the onset of premature ventricular contractions during surgery signifies an increase in blood pressure, a difficulty which may be reversed by increasing the rate of administration of phentolamine. Should this fail, 75 to 100 mg. of lidocaine may be administered intravenously or the level of anesthesia may be deepened by using halothane. Propranolol in a dosage of 1 to 5 mg. intravenously rarely accomplishes more than the preceding maneuvers.

In abdominal pheochromocytomas, laparotomy is carried out through an upper adbominal incision the type of which (midline or transverse) depends on the configuration of the costal arches. Following inspection and palpation of the abdominal viscera, the suprarenal glands are exposed formally. The right adrenal is explored after mobilization of the duodenum and exposure of the segment of the cava near the upper pole of the kidney. The left adrenal gland is approached through the lesser sac (via the hepatogastric or gastrocolic ligaments) or through the transverse mesocolon. The lateral approach by mobilization of the splenic flexure of the colon can be used if this segment of the colon can be mobilized

abdomen the majority of the rest being not only located within the chest but almost always visible upon careful roentgenographic evaluation. This must include posteroanterior, lateral, and both anterior oblique views of the chest and, should doubt remain, tomography as well. Despite reports to the contrary,[8,25] this laboratory and at least one other[4] have studied patients in whom the relative excretion of F as opposed to NE or of M as opposed to NM failed to correlate with the location of their pheochromocytoma.

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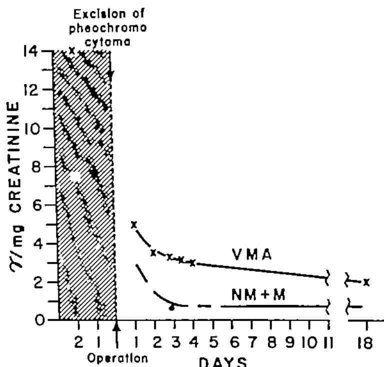


Fig. 2 Return to normal of catecholamine catabolite excretion following surgery for pheochromocytoma. γ/mg. creatinine = μg/mg. creatinine.

excretion (Fig 2) Postoperative hemorrhage or infection may result in protracted elevation of TM excretion but will rarely elicit an increase in VMA excretion above 5 μg per milligram creatinine after the second postoperative day

Postoperative surgical sepsis is best treated initially with one of the antibiotic agents effective against hospital-acquired *Staphylococcus aureus* until specific bacteriologic studies are available. The majority of infections in the wound or in the subphrenic spaces are indeed due to this organism. Infection in the subphrenic spaces is usually heralded by a homolateral pleural effusion Diagnostic aspiration of pleural fluid is helpful in determining the presence or absence of bacteria. An elevated amylase concentration with a left pleural effusion may rarely result from a pancreatitis due to surgical trauma.

It is imperative that children patients with a neurocutaneous syndrome, multiple endocrine neoplasia, or familial pheochromocytoma be periodically evaluated for postoperative recurrence of a neural crest lesion. Such lesions are usually observed within two years of initial surgery

Conclusion

Advances in our knowledge of the biochemistry of human catecholamine metabolism have led to a degree of diagnostic accuracy which should result in the detection of tumors of neural crest origin in the overwhelming majority of patients. Since over 90 per cent of pheochromocytomas are histologically benign, appropriate medical and surgical management should effect a cure in the majority of such patients. Although the biochemical and therapeutic tools are readily available for the management of these patients, the inexperienced or unsuspecting physician may still fail to protect them from the explosive and often fatal consequences of their disease. It is to be urged that broad screening programs be implemented for detection of pheochromocytomas and that a team consisting of an internist, anesthesiologist, and surgeon, possessing considerable experience in this particular field be relied upon for pre-

easily without damaging the spleen Even though the authors prefer the approach through the lesser sac (remaining below the pancreas) the wide topographic variability of the viscera in this region demands knowledge of all possible avenues of dissection In our experience it has not been necessary to extend the incision into the thorax to provide adequate exposure of the suprarenal areas.[43, 44]

One should avoid immediate resection of the first adrenal tumor to be exposed until an examination of the contralateral adrenal offers evidence regarding the need to exercise care for conservation of adrenal tissue Following exploration of both adrenals, *it is essential to* look for ectopic neural crest tumors arising anywhere in the abdomen the most frequent sites being the celiac axis region the para-aortic areas the aortic bifurcation (organ of Zuckerkandl) and the uretero vesicular junctions. It is this completeness of exploration made possible through the anterior transperitoneal approach that can never be accomplished by either the posterior or the flank incisions. Most of the bleeding problems can be avoided if the main adrenal vein is ligated and divided first and if the arterial branches from the inferior phrenic arteries are treated carefully Complete hemostasis is paramount not only during the phase of transient hypotension that follows resection of the tumor but also after restoration of normal arterial pressure A dry operative field with a systolic blood pressure of 85 mm Hg can become a pool of blood with a pressure of 130 mm Hg Moreover neural crest tumors are vascular and α blocking drugs tend to promote venous oozing The control of retroperitoneal bleeding remains one of the major concerns in the surgical care of these patients.[41]

Complete removal of the tumor(s) is usually followed by a fall in arterial pressure down to hypotensive levels this can be corrected in most instances by increasing the rate of albumin infusion thus avoiding the use of vasopressors. In malignant pheochromocytomas an attempt to resect as much of the tumor as possible may reduce the total secretory capacity and thus facilitate the postoperative pharmacologic management. It has been our practice to close the abdomen without drainage in two layers using absorbable sutures for the peritoneum and nonabsorbable material for the fascial layer Mediastinal neural crest tumors are resected through a posterolateral thoracotomy while the rare pheochromocytomas in the neck are removed through appropriately placed incisions.

Postoperative management

Monitoring of the cardiac rate and rhythm as well as arterial and central venous pressure monitorings are continued through the immediate postoperative period The hourly urinary output is measured and is considered a more reliable index of renal and tissue perfusion than the actual level of systolic arterial pressure. Pharmacologic support for borderline hypotension is not necessary as long as urinary output remains adequate *Persistent hypotension* in the immediate postoperative period in the face of adequate volume replacement during surgery suggests bleeding at the operative site[41] or less likely a cardiogenic cause *Administration* of pressor agents in a futile attempt to maintain the blood pressure cannot but result in a disaster in the presence of retroperitoneal hemorrhage.

Postoperative hypertension is usually due to residual neural crest tumor(s) a fluid overload or complicating essential hypertension Fluid balance will invariably correct itself resulting in a gradual decrease in blood pressure and pulse rate during the first few postoperative days. Whether residual hypertension is related to an unresected neural crest lesion or to the added complication of essential hypertension which may legitimately be expected in from 10 to 20 per cent of the patients the blood pressure elevation is nevertheless lower than that noted preoperatively and requires either no medication or minimal amounts of antihypertensive drugs. Modest quantities of benzothiadiazides, α-methyl dopa guanethidine or spironolactone will not seriously compromise the reliability of assays of the catecholamine catabolites during the postoperative period Complete resection of the neural crest lesion usually results in a prompt fall in VMA and TM

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should be known and should be consistent if daily comparisons are desired. Renin and the angiotensins are labile at room temperature in vitro in the presence of either whole blood or plasma. Blood should always be drawn into iced tubes containing the anticoagulants and/or enzyme inhibitors specified by the laboratory doing the assay. The blood must be spun down in the cold and the plasma frozen within few hours to avoid substantial losses.

Two of the best known causes of remediable hypertension can be diagnosed from abnormalities in renin activity and aldosterone production.[illegible] I primary aldosteronism, excessive and autonomous secretion of aldosterone is mediated by an adrenal cortical adenoma or hyperplastic adrenal glands. The aldosterone causes salt and water retention and suppresses renin secretion. If sodium intake is adequate, renal potassium excretion is excessive and serum potassium is low. Renin activity is low and cannot be stimulated by posture, salt depletion, or diuretics. The diagnosis of primary aldosteronism requires the demonstration of increased aldosterone production in addition to suppressed renin. Not all patients with suppressed renin have primary aldosteronism. Ten to 40 per cent of patients with essential hypertension do not elevate renin levels in response to ordinary stimuli.[illegible] These patients are normokalemic and have normal aldosterone production. Increased extracellular fluid volume[illegible] and increased intravascular pressure at the level of the juxtaglomerular cells[illegible] have been described in this group. The production of abnormal mineralocorticoid(s) has been implicated in the pathogenesis of this syndrome.[illegible]

I renovascular hypertension, renin secretion is increased because of impaired glomerular perfusion. The increased angiotensin II produced stimulates aldosterone secretion, resulting in secondary aldosteronism. The peripheral vein renin activity in either basal or stimulated state is an unreliable screening test. Most published series report an incidence of 30 to 50 per cent of normal peripheral vein renin activity in patients with proved renal artery stenosis who were improved by operation. The differential renal vein renin determination is the most reliable diagnostic test for evaluating the functional significance of unilateral renal artery stenosis and predicting the outcome of surgical treatment. When renin activity on the side of the lesion is above normal and greater than 1.5 times that of the uninvolved side, the probability of improvement in blood pressure after operation is 90 per cent.[illegible] The differential renal vein renin test should be done after stimulation of renin release, since the kidney on the side of the lesion is selectively stimulated. Tilting, salt deprivation, vasodilators, and diuretics have been used successfully as provocative stimuli without significant incidence of false positives. It has been demonstrated that cases of significant unilateral renal artery stenoses can be missed if renal vein sampling is done in the unstimulated state.[illegible] The evaluation of patients with bilateral disease is more complex and requires correlation of renin determinations with split renal function tests and, in some cases, renal hemodynamic studies.

The renin activity assay when pplied in a carefully controlled fashion, is a usef l screening test for treatable causes of hypertension. Suppressed renin activity accompanied by elevated aldosterone is diagnostic of adrenal hyperplasia or adenoma. Suppressed renin with normal aldosterone is seen in many patients with apparent essential hypertension though additional etiologic diagnoses of hypertension may be found in this group as a result of further research. I the patient with significant unilateral renovascular disease renin activity is elevated in the venous effluent of the involved kidney but not necessarily peripheral venous blood. This provides the most accurate predictive test of surgical cure in this syndrome.

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Annotations

Renin in differential diagnosis of hypertension

New methods of measuring small peptides in the circulation have advanced our understanding of the renin-angiotensin-aldosterone system in physiologic and pathologic states. Radioimmunoassays for angiotensin II and I have proved useful as screening tests for treatable causes of hypertension since the relative ease in performing these tests, as well as their productivity allows more widespread application. A brief review of the biochemistry and physiology of the renin-angiotensin system may set in perspective its possible role in the genesis of hypertensive disease.

Renin is a proteolytic enzyme secreted by the kidney. Its only known function is to act on a substrate protein in plasma to release angiotensin I, a physiologically inactive decapeptide. The decapeptide is enzymatically converted to angiotensin II, a physiologically active octapeptide. The most important site of in vivo conversion is the pulmonary capillary bed,[1,2] with the kidney participating to a lesser extent. The lungs have a very large capacity for converting angiotensin I in a single passage. Plasma contains a converting enzyme which is responsible for in vitro conversion, but acts too slowly to be an important in vivo mechanism. Angiotensin II is a potent pressor agent and a direct stimulator, even at subpressor levels, of aldosterone production. Angiotensin II is rapidly removed from the circulation by a combination of enzymatic degradation[4] and sequestration in the peripheral capillary beds.

Techniques for the direct measurement of renin content of human blood are not available at the present time. Renin levels are generally determined indirectly by measuring renin activity, the rate of release of angiotensin I or II from renin substrate in an in vitro incubation system. The peptides generated are then measured by bioassay or radioimmunoassay. The quantities of angiotensin peptides generated in a renin activity assay are several hundred times the levels of angiotensin circulating in plasma and are thus much easier to measure. The most sensitive, specific, and reproducible determinations of renin activity employ a radioimmunoassay for angiotensin I.[5] Enzyme inhibitors are added to block both plasma converting enzyme and angiotensinases. The complex extraction steps and system of internal standards which were required for most angiotensin II assays are obviated in the angiotensin I assay.

Circulating levels of angiotensin II have been measured directly with the use of high-affinity antibody.[8] Normal values are less than 50 picograms per milliliter of plasma.[9-11] Levels of circulating angiotensin II correlate well with renin activity. The concentration of angiotensin I in circulating blood cannot be measured directly by immunoassay because of nonspecific cross-reactive materials in plasma.[12]

In normal man and in most hypertensive patients, renin secretion is sensitive to intravascular volume and sodium content and to renal perfusion pressure. The assumption of the upright posture, hemorrhage, sodium restriction, and the administration of diuretics all tend to increase renin levels. Volume expansion and sodium intake tend to decrease renin activity.

Renin release is labile, and changes in plasma renin activity following some of these stimuli can be large. In normal subjects, peripheral and renal vein renin activity rises by a factor of three within 20 minutes of passive upright tilting and returns to base-line levels within 30 minutes of return to the horizontal position.[13] The postural augmentation of renin release correlates with increases in aldosterone[1] and catecholamine[14] production and excretion and with changes in renal hemodynamics. On assumption of the upright posture, blood pools in the lower extremities, decreasing the effective blood volume. Renal blood flow and glomerular filtration rate fall despite the maintenance of central arterial pressure, suggesting that renal vasoconstriction takes place. Decreased blood flow to the glomerulus stimulates renin release. After three days of strict sodium restriction, supine renin levels increase by a factor of 2; upright renin levels, by a factor of 6. Acute diuretic administration causes a tenfold increase in plasma renin activity.[8] During chronic diuretic administration at constant dosages, in hypertensive patients, renin activity gradually falls and plasma volume rises nearly to normal levels. The nondiuretic antihypertensive drugs hydralazine,[8] diazoxide, and nitroprusside[16] cause a rise in plasma renin activity by mechanisms which have not been fully elucidated. Alpha-methyldopa has been reported to lower renin activity, presumably by producing a partial adrenergic blockade.[16] Estrogens stimulate the hepatic production of renin substrate, and renin activity increases secondarily.[17] These changes are seen at estrogen levels achieved with the commonly used oral contraceptive agents and occur whether or not hypertension is produced. For these reasons, it is necessary to know the posture and salt and drug intake of each patient at the time of renin determination. Since there is a diurnal variation of renin release,[18] the time of blood drawing

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shown that the most conspicuous and disabling neurological feature is the Parkinson syndrome. Symptomatic postural hypotension is uncommon in untreated parkinsonian patients but a continuous spectrum may exist from primary idiopathic orthostatic hypotension on one hand to classical parkinsonism on the other. Barbeau and associates[4] have investigated the role of the renin-aldosterone systems in parkinsonians and have shown low plasma renin activity with parallel decrease in aldosterone secretion.

The pressor effects of intravenous L-dopa in man were first demonstrated in 1942[26] and it was anticipated that the administration of large oral doses of catecholamine precursor would cause hypertension. Indeed synchronous administration of L-dopa with monoamine oxidase inhibitors causes a dramatic rise in blood pressure which can be controlled with alpha-adrenoreceptor blockers.[11] However chronic medication with L-dopa alone lowers both the systolic and diastolic blood pressures in the erect and supine positions in many patients, without significant change in the pulse rate. In one study the blood pressure was lowered by at least 30 mm. Hg in 85 per cent of the patients.[9] L-dopa-induced hypotension is usually asymptomatic and pressures tend to return to normal during the second or third month of treatment[7] occasionally even with very small drug increments, persistent hypotension may be barrier to further treatment and disabling hypotension has been observed even after 8 months on L-dopa.[16] Mild hypotensive symptoms such as lightheadedness have been reported in 4 to 23 per cent of the patients[1,2,14] rarely serious complications such as myocardial or cerebral infarction[7] have occurred which have been attributed to severe hypotension. For these reasons, patients with evidence of cardiac or cerebral ischemia were excluded from early therapeutic trials[8] and it is possible that more extended observations in unselected patients will reveal greater hazards of this nature. During therapy hypotension in vulnerable subject can often be minimized by cautiously increasing the dose of -dopa mild symptoms can be alleviated by elastic stockings[8,15,16] or bed rest[11] and more distressing disturbances have been relieved by the administration of 3 Gm. of sodium chloride, daily.[15] The use of salt-retaining steroids such as fludrocortisone has yet to be fully explored.

The possible mechanisms of -dopa-induced hypotension in parkinsonian patients have aroused much speculation. To investigate the possibility that increased peripheral dopamine is responsible, pupil size has been studied[13] on the assumptions that changes are directly due to actions on the alpha-adrenoreceptors of the dilator pupillae muscle and that such changes accurately reflect alterations of generalized vasomotor tone. Dopamine installation into the conjunctival sac causes mydriasis which can be inhibited by pretreatment with guanethidine, a drug hich depletes noradrenaline stores the indirectly acting sympathomimetic tyramine behaves similarly.[13] These findings, although disputed,[16] suggest that the peripheral effects of dopamine are dependent upon the integrity of adrenergic nerve endings. The mydriasis produced by conjunctival dopamine gradually wanes after prolonged application but, as local phenylephrine is still effective, this phenomenon cannot be ttributed to alpha-receptor blockade, and it is more likely to be due to depletion of noradrenaline stores. It has therefore been suggested that, as a consequence of L-dopa administration, dopamine displaces nor adrenaline t nerve endings thereby diminishing the physiological consequences of nerve impulse. This hypothesis is supported by isotope uptake studies in rabbits[28] and could account for the meiosis seen in patients who have been treated with L-dopa for several weeks.[29]

It has also been suggested that metabolites of L-dopa other than dopamine might cause hypotension. Sandler[30] has postulated that 6-hydroxydopamine or similar compound may cause neuronal degeneration in parkinsonism; this might provide a central or peripheral basis for induced hypotension. It is also possible that L-dopa which readily crosses the blood-brain barrier may have direct effect on the vasomotor system. The use of a peripheral decarboxylase inhibitor would be expected to enhance central effect whereas, if hypotension is due to peripheral dopamine, there should be less effect upon blood pressure.[16] There has been insufficient recorded experience of the effects of peripheral decarboxylase inhibitors and L-dopa upon blood pressure and this point waits clarification. Possible involvement of renin-aldosterone systems has also been considered low plasma renin activity is further decreased by L-dopa therapy[4] and there is evidence that the system is slow to react. However while renin-aldosterone systems are important in the postural control of blood pressure,[31] their malf ac tion is unlikely to account for sustained hypotension. Whatever the complexity of mechanisms underlying the hypotensive effect of L-dopa in parkinsonian patients, an acceptable explanation must also c count for the absence of hypotension when L-dopa is given to normal subjects.[26,32]

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Parkinsonism and the hypotension caused by L-dopa

Following the pioneer observations of Ehringer and Hornykiewicz[1] that the basal ganglia of patients with Parkinsonism are focally deficient in dopamine, an effective oral treatment using the immediate precursor L-d hydroxyphenylalanine (L-dopa) has been developed. Many parkinsonian patients have now been treated with L-dopa and it may be timely to review the associated disturbances of blood pressure. Parkinsonian patients, particularly those with akinetic disabilities, have a blood pressure of 15 to 20 mm. Hg below the average for their age group.[2,3] The pathophysiology of this hypotension has yet to be fully explained. Isotope studies in patients with idiopathic parkinsonism indicate decreased noradrenaline metabolism and increased dopamine catabolism[4] and as similar findings have been described in neurogenic orthostatic hypotension, a defective noradrenaline synthesis in peripheral sympathetic nerve endings has been presumed In the first issue of this JOURNAL, Bradbury and Eggleston[7] delineated the clinical entity of primary orthostatic hypotension more recently there has been renewed interest in this problem and particular attention has been directed to associated structural changes in the central nervous system. Shy and Drager[8] have described defects in blood pressure control in relationship to a Parkinson-like syndrome and Thomas and Schirger in an extensive study of patients with idiopathic orthostatic hypotension and neurological defects, have

shown that the most conspicuous and disabling neurological feature is the Parkinson syndrome. Symptomatic postural hypotension is uncommon in untreated parkinsonian patients but continuous spectrum may exist from primary idiopathic orthostatic hypotension on one hand to classical parkinsonism on the other. Barbeau and associates[4] have investigated the role of the renin-aldosterone systems in parkinsonians and have shown low plasma renin activity with parallel decrease in aldosterone secretion.

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Parkinsonism and the hypotension caused by L-dopa

Following the pioneer observations of Ehringer and Hornykiewicz that the basal ganglia of patients with Parkinsonism are focally deficient in dopamine, an effective oral treatment using the immediate precursor L-dihydroxyphenylalanine (L-dopa) has been developed[1] Many parkinsonian patients have now been treated with L-dopa and it may be timely to review the associated disturbances of blood pressure. Parkinsonian patients, particularly those with akinetic disabilities, have a blood pressure of 15 to 20 mm. Hg below the average for their age group. The pathophysiology of this hypotension has yet to be fully explained Isotope studies n patients with idiopathic parkinsonism indicate decreased noradrenaline metabolism and increased dopamine catabolism[4] and as similar findings have been described in neurogenic orthostatic hypotension a defective noradrenaline synthesis in peripheral sympathetic nerve endings has been presumed In the first issue of this JOURNAL, Bradbury and Eggleston delineated the clinical entity of primary orthostatic hypotension more recently there has been renewed interest in this problem and particular ttention has been directed to associated structural changes in the central nervous system. Shy od Drager[4] have described defects in blood pressure control in relationship to a "Parkinson-like syndrome and Thomas and Schirger in an extensive tudy of patients with idiopathic orthostatic hypotension and neurological defects, have

patients with Raynaud' disease and phenomenon was also noted. This reduction in superficial digital blood supply and limited vascular reactivity has been demonstrated using different systems by others[4] and is compatible with either increased autonomic nervous system activity small vessel intrinsic obstructive disease or both. Sympathetic nervous system "hypoactivity has been demonstrated in some patients with Raynaud phenomenon. This may conceivably be an attempt t compensate for reduced digital blood flow that is secondary to small vessel obstructive disease.

Thirteen patients were given intra-arterial reserpine 0.6 mg into either the radial or brachial artery of one upper extremity Heat loss measurements were made both before and after treatment with reserpine. In those who responded to the reserpine, heat-loss measurements were repeated periodically thereafter (usually weekly) until mean values returned to baseline levels. Seven of the 13 patients demonstrated both subjective and objective responses lasting from one day to six weeks with mean duration of 18 days. Among those improving, the most marked improvement i heat loss measurements was noted in the injected arm in nearly every instance. The opposite extremity usually improved but to lesser degree than the injected side. I association with the improvement in the heat-loss pattern the patients described feeling of increased warmth in the injected extremity nd disappearance of color change in their hands after cold exposure and emotional stimuli. I some there was marked erythema of the injected extremity one and one-half to two hours after receiving reserpine followed soon thereafter by erythema on the contralateral side. The erythema had usually disappeared 24 to 36 hours later One patient given repeat intra-arterial injection of reserpine, several months after the initial response had disappeared, had nearly identical improvement the second time. I travenous reserpine (0.6 mg.) was given to one patient with subjective improvement in superficial digital blood flow that lasted three days. Two patients initially responding to the intra-arterial injection were given oral reserpine (0.25 mg. per day) for four to six weeks. Oral reserpine in the doses used was ineffective in producing either subjective or objective improvement. This may however be related to the relatively small oral dose used in our study Others, using larger oral doses, have reported improvement in treating Raynaud' disease patients. Oral methyldopa (Aldomet) and guanethidine (Ismelin) in sufficient amounts have also been demonstrated to be effective in preventing episodes of Raynaud' phenomenon during cold weather and in improving blood supply to digital skin during cold exposure.[5,6]

Reasons for improvement in superficial digital blood flow after parenteral reserpine cannot be stated with certainty Either catecholamine or serotonin depletion[7] could be responsible. The factors that result in the limited period of improvement after reserpine are unknown but presumably the return of catecholamine and/or serotonin influence over digital blood vessels is involved. I those patients not responding to the intra-arterial reserpine in our study it ppeared that significant fixed intravascular or extravascular obstructive disease was present to the degree that lessening of autonomic nervous system control was of no appreciable benefit. Reserpine and other catecholamine nd/or serotonin depleters or inhibitors are useful in providing t least temporary benefit from signs and symptoms of the digital vascular insufficiency in some patients with Raynaud disease. I some of those patients able to tolerate relatively large oral doses of reserpine, guanethidine, or aldomet prolonged improvement in digital blood flow ca be provided. These agents may also be helpful in the future in elucidating pathogenetic differences between patients with Raynaud' ttacks

Parenteral reserpine and the oral catecholamine depleting agents, demonstrated to be of benefit in ameliorating the signs and symptoms of the Ray naud process, should be used only in patients with incapacitating symptoms. Those patients with recurrent digital ulcerations, vasospastic attacks ac companied by severe pain, nd/or digital gangrene are candidates for parenteral as well as oral catecholamine depleting therapy Those patients with less severe Raynaud' ttacks should be advised to void undue digital trauma, keep their hands as warm as possible, and discontinue smoking if the latter is their practice.

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Raynaud's disease and phenomenon, a medical approach

Raynaud's disease and phenomenon are the cause of severe symptoms in some patients. Treatment of the underlying connective tissue disease, when that is the etiology of Raynaud's phenomenon, usually does not influence the frequency or severity of vasospastic phenomena.

Recently intra-arterial reserpine has been reported to ameliorate some of the signs and symptoms in patients with Raynaud's disease and phenomenon.[1] We have recently reported the results of our own studies of treating these patients with reserpine utilizing a heat loss measuring instrument as an indirect but objective measure of superficial digital blood flow

The heat loss studies were carried out in both normal control patients and patients with Raynaud's disease and phenomenon at rest, during cold exposure, and upon return to room temperature following the exposure to cold. Statistical analysis of the heat loss patterns demonstrated significant differences in mean superficial digital heat loss at rest during exposure to cold, and after return to room temperature between the controls and patients. Limited vascular reactivity to environmental changes in the

patients with Raynaud's disease and phenomenon was also noted. This reduction in superficial digital blood supply and limited vascular reactivity has been demonstrated using different systems by others[3] and is compatible with either increased autonomic nervous system activity, small vessel intrinsic obstructive disease, or both. Sympathetic nervous system "hypoactivity" has been demonstrated in some patients with Raynaud's phenomenon. This may conceivably be an attempt to compensate for reduced digital blood flow that is secondary to small vessel obstructive disease.

Thirteen patients were given intra-arterial reserpine 0.6 mg. into either the radial or brachial artery of one upper extremity. Heat loss measurements were made both before and after treatment with reserpine. In those who responded to the reserpine, heat-loss measurements were repeated periodically thereafter (usually weekly) until mean values returned to baseline levels. Seven of the 13 patients demonstrated both subjective and objective responses lasting from one day to six weeks with a mean duration of 18 days. Among those improving, the most marked improvement in heat-loss measurements was noted in the injected arm in nearly every instance. The opposite extremity usually improved but to a lesser degree than the injected side. In association with the improvement in the heat-loss pattern the patients described a feeling of increased warmth in the injected extremity and disappearance of color change in their hands after cold exposure and emotional stimuli. In some there was marked erythema of the injected extremity one and one-half to two hours after receiving reserpine followed soon thereafter by erythema on the contralateral side. The erythema had usually disappeared 24 to 36 hours later. One patient given a repeat intra-arterial injection of reserpine, several months after the initial response had disappeared, had nearly identical improvement the second time. Intravenous reserpine (0.6 mg.) was given to one patient with subjective improvement in superficial digital blood flow that lasted three days. Two patients initially responding to the intra-arterial injection were given oral reserpine (0.25 mg. per day) for four to six weeks. Oral reserpine in the doses used was ineffective in producing either subjective or objective improvement. This may however be related to the relatively small oral dose used in our study. Others, using larger oral doses, have reported improvement in treating Raynaud's disease patients. Oral methyldopa (Aldomet) and guanethidine (Ismelin) in sufficient amounts have also been demonstrated to be effective in preventing episodes of Raynaud's phenomenon during cold weather and in improving blood supply to digital skin during cold exposure.

Reasons for improvement in superficial digital blood flow after parenteral reserpine cannot be stated with certainty. Either catecholamine or serotonin depletion[6,7] could be responsible. The factors that result in the limited period of improvement after reserpine are unknown but presumably the return of catecholamine and/or serotonin influence over digital blood vessels is involved. In those patients not responding to the intra-arterial reserpine in our study it appeared that significant fixed intravascular or extravascular obstructive disease was present to the degree that lessening of autonomic nervous system control was of no appreciable benefit. Reserpine and other catecholamine and/or serotonin depleters or inhibitors are useful in providing at least temporary benefit from signs and symptoms of the digital vascular insufficiency in some patients with Raynaud's disease. In some of those patients able to tolerate relatively large oral doses of reserpine, guanethidine, or aldomet prolonged improvement in digital blood flow can be provided. These agents may also be helpful in the future in elucidating pathogenetic differences between patients with Raynaud's attacks.

Parenteral reserpine and the oral catecholamine depleting agents, demonstrated to be of benefit in ameliorating the signs and symptoms of the Raynaud's process, should be used only in patients with incapacitating symptoms. Those patients with recurrent digital ulcerations, vasospastic attacks accompanied by severe pain, and/or digital gangrene are candidates for parenteral as well as oral catecholamine depleting therapy. Those patients with less severe Raynaud's attacks should be advised to avoid undue digital trauma, keep their hands as warm as possible, and discontinue smoking if the latter is their practice.

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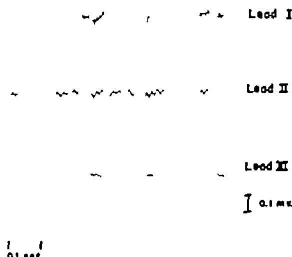
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The electrocardiogram of the Drosophila

In a study of aging of the heart of the *Drosophila repleta* Wollaston[1,2] electrocardiograms were recorded in an attempt to learn whether or not it was possible to correlate the ultrastructural changes with electrophysiologic ones. The resulting tracings were considered interesting and might be of interest to others. They were obtained with electronic circuits and equipment with adequate fidelity for recording frequencies at least as high as 4 × 10³ Hz. The tracings described here were recorded with three sharp needle electrodes placed on the lateral aspect of the thorax and ventral posterior aspect of the abdomen to approximate the Einthoven equilateral triangle system of electrode placement. Recordings obtained were arbitrarily designated standard Leads I, II and III. The flies were prepared by injuring their brains with a sudden blow and they were laid supine for the recordings.

The heart of the Drosophila consists of a series of four chambers and is located in the dorsal aspect of the abdomen extending from the sixth abdominal segment to the mesophragma.[3] Two recordings from the same fly are illustrated. One recording (Fig. 1, 1) obtained immediately after the fly was pre-

A.) Immediately after placing electrodes



B.) 5 minutes after placing electrodes

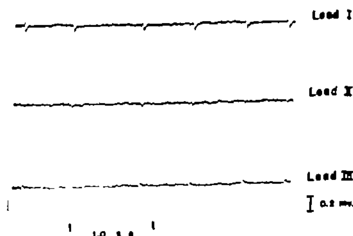


Fig. 1. Electrocardiogram of *Drosophila repleta* Wollaston.

pared shows an irregular deflection rate of approximately 1,800 per minute. The cardiac mechanism probably represents a complexity of multiple parasystolic rhythms. The irregular isoelectric baseline is due to extracardiac muscle movement. The recording in Fig. 1 *B* was obtained about 5 minutes later (approximately one hour after the brain was first injured) when the fly was dying and the cardiac rhythm was regular with a deflection rate of 102 per minute. There was no extracardiac muscular electric background from movement of the wings and limbs of the dying fly

There were considerable variations in the cardiac mechanism and configuration of the complexes from fly to fly but the general appearance of the electrocardiogram was similar in all flies. Various rhythm disturbances were noted. The tracings were easy to obtain. The heart of the Drosophila could serve as useful research model.

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Letters to the Editor

Long-chain saturated fatty acid (FFA) and sudden death in myocardial infarction

To the Editor

Over the last decade there has accumulated a large amount of information as to the relationship of the chemical constituents of the blood to coronary artery disease and sudden death No one mechanism explains these relationships and the problem appears to be multifactorial in nature. One such relationship was reported between the serum-free fatty acid level and the frequency of serious arrhythmias among patients in the coronary care unit[1] but other workers[2] were unable to confirm the above findings. However there is evidence to show that high serum-free fatty acid level does have a deleterious effect on the heart, and this has been thought to be related to a depressant influence on myocardial metabolism resulting in ins fficient energy substrates.[3,4] On the other hand Henderson and associates[5] suggested that the adverse effect of FFA on the heart may be due to a detergent effect or due to a calcium binding in the myofibrils, rather than to a reduction of high energy stores. These observations were based on the finding of depressed contractility of the hypoxic rat papillary muscle with FFA. We have also observed a similar association between decreased cardiac contraction and infusion of free fatty acid into the coronary artery during experimental myocardial hypoxia and inf rction

Experiments were carried out in 11 lightly-sedated closed-chest dogs. Partial occlusion of the left coronary artery (circumflex branch in 5 dogs, a terior descending branch in 6) was produced by selective placement of a magnesium helical coil wire The coil produces 5 to 10 per cent obstruction of the artery and being thrombogenic n nature a partial to-complete occlusion at the wire site usually occurs w thin 4 to 6 hours. A special double-lumen catheter was passed via the left common carotid artery for wire placement The coronary arteries were visualized by njection of ngio dye through the inner catheter under fluoroscopy The methodology of wire placement has been described in detail elsewhere. Two to 4 ml of 1 1000 w /v suspension palmitic acid was injected into the coronary artery in 2 to 4 seconds. FFA was injected one-half hour after wire placement in five dogs (Group I) six hours after wire placement in four dogs (Gro p II) and 2 to 10 days after placement n two dogs (Group III) These three groups represented different tages of coronary occlusion—from cute myocardial hypoxia to 10-day-old myocardial infarct. The observations were made with continuous electrocardiographic monitoring and cardiac silhouette determination under fluoroscopy Fifteen to 20 seconds following injection of FFA into the coronary artery all the dogs in Group I and Group III and two dogs in Group II showed dilatation of the heart and almost complete loss of contractility under fluoroscopy The pulse and blood pressure were not obtainable at the end of two minutes. Resuscitative efforts were of no avail and complete mechanical standstill, absence of blood flow and terminal arrhythmias occurred within three to four minutes. The other two animals in Group II which did not die at first injection of FFA lived for 5 and 10 days, respectively At this time a repeat coronary arteriography showed 75 to 90 per cent occlusion of the respective coronary arteries at the wire site and injection of 2 mL of FFA into the coronary artery produced immediate death of the animals with cardiac standstill. The ECG changes observed in the entire study were immediate acute ST segment elevation with NSR 15 to 20 seconds after FFA injection. Later it changed to supraventricular tachycardia or sinus bradycardia ending in sinus arrest with slow idioventricular rhythm. In six of the dogs intraventricular conduction defects and complete heart block were observed 3 to 5 min tes after FFA injection. The terminal arrhythmias were ventricular fibrillations or systole These ECG findings are in agreement with earlier experimental and clinical reports. However as shown, these serious arrhythmias appeared subsequent to myocardial failure.

The clinical implications of these observations, if any are that dur g acute myocardial hypoxia or infarction sudden rise in blood FFA level may markedly depress myocardial contractility leading to drop in cardiac output and ending in serious arrhythmias. Recent observations that physiological concentrations of FFA have a marked depressant effect on the perfused rat heart under hypoxic conditions further corroborate our findings and suggest a plausible mechanism.

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An appraisal of Starr-Edwards valve replacement after a decade

T the Editor

On Sept. 21 1960, the first successful heart valve replacement was performed. On that date young man severe calcific mitral regurgitation was relieved with caged-ball prosthesis t the University of Oregon Medical School. Since then, some 75,000 Starr Edwards valves have been delivered for implantation, and their effectiveness continues to make them standard by which all others are judged. Detailed follow-up studies by the Oregon group now span decade of experience with more than 1000 patients, providing scientific basis for advising surgical treatment for the patient who continues to suffer from the effects of valve dysfunction despite medical therapy

What outcome does this operation offer t present? The author answers this question from the viewpoint of the practicing cardiologist, based primarily on the care of 91 private patients who have had ball-valve replacement by various surgeons since 1963 and based secondarily on his experience since 1956 as visiting member of the Division of Cardiology t the University of Oregon Medical School.

The outlook for pleasing surgical result approaches 65 per cent, with moderate to marked increase in bodily function resulting from the hemodynamic improvement. The median duration of this aftercourse statistically is nine years, being longer in those patients ho are young or who have had no complicating disease. Current actuarial studies suggest that the better mitral (and possibly aortic) patients in the 50 to 64 year age group will be eligible for a permanent lif insurance plan at moderately increased premium.

Unsatisfactory courses after surgery may be anticipated in one third of cases

Fifteen per cent die before recovering fully from the operation. More of these deaths occur in older nd in sicker patients and ith less experienced surgical and nursing teams.

Ten per cent are not materially relieved of cardiac symptoms. The causes for this are (1) residual myocardial, vascular or valvular disease that may or may not have been diagnosed or correctible (2) the implantation of an inadequate prosthesis (e.g., in an adult with small aortic ring, the use of child-size prosthesis may prove insufficient in relieving the tenosis) (3) inadequate surgical technique that may result in [a] paravalvular leak about the valve ring (in 10 per cent or less of the cases) or in the struts eroding an adjacent structure [b] damage to the conduction system, the myocardium, or an artery while the patient is on cardiopulmonary bypass—reoperation (done in 5 per cent of the cases) may correct one of these faults nd (4) an associated operation, e.g coronary artery reconstruction, may be unsuccessful.

Five per cent sustain permanent serious neurological damage during or after surgery Hemiplegia and visual loss are the principal manifestations. Embolism of air calcific particles, or thrombus are the usual causes, although the incidence of each is probably declining. Persistent psychosis rarely has developed.

The remaining 5 per cent of unsatisfactory results are due to one or more of the following causes severe hemolytic nemia (which is seen over all in 1 per cent of valve replacement patients) endocarditis (the rate of which is 0.5 per cent per year), complications of anticoagulant therapy chronic hepatitis from drug or blood sources, and disabling fracture from fall in the postoperative period.

Late deaths, which may come soon enough to constitute an unsatisfactory result, now occur t the rate of 5 per cent per year—mainly from coronary artery disease and silastic ball variance (seen in the 1000 Series valve almost exclusively) in the aortic cases, and from thromboembolism or infection in the mitral patients. Two of these causes appear to have been largely controlled, because the silastic poppet has been replaced by stellite alloy which has functioned flawlessly for periods of over three years, and the cloth-covered valves seldom have given rise to thromboembolism (even when anticoagulants have not been used).

Thus, for most patients, valve replacement means a restoration to reasonably active life. The three-month operative recovery period, the necessity for continued medical ttention (with attendant expense) an average of monthly care as an outpatient and perhaps biennial hospitalization, the prohibition of potentially traumatic activities such as skiing and diving, the frequent awareness of the metal ball" movement in the cage—all these are generally accepted with the acknowledgment that the lif span has been both broadened and lengthened by means of these marvelous valves.

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"Cannon waves" in complete A-V block

T the Editor

A valuable sign for the clinical diagnosis of complete A-V block is the irregular occurrence of an

Letters to the Editor

Long-chain saturated fatty acid (FFA) and sudden death in myocardial infarction

To the Editor

Over the last decade there has accumulated a large amount of information as to the relationship of the chemical constituents of the blood to coronary artery disease and sudden death. No one mechanism explains these relationships and the problem appears to be multifactorial in nature. One such relationship was reported between the serum-free fatty acid level and the frequency of serious arrhythmias among patients in the coronary care unit, but other workers were unable to confirm the above findings. However, there is evidence to show that high serum-free fatty acid level does have a deleterious effect on the heart and this has been thought to be related to a depressant influence on myocardial metabolism, resulting in insufficient energy substrates.[3,4] On the other hand, Henderson and associates[5] suggested that the adverse effect of FFA on the heart may be due to a detergent effect or due to a calcium binding in the myofibrils rather than to a reduction of high energy stores. These observations were based on the finding of depressed contractility of the hypoxic rat papillary muscle with FFA. We have also observed a similar association between decreased cardiac contraction and infusion of free fatty acid into the coronary artery during experimental myocardial hypoxia and infarction.

Experiments were carried out in 11 lightly sedated closed-chest dogs. Partial occlusion of the left coronary artery (circumflex branch in 5 dogs, anterior descending branch in 6) was produced by selective placement of a magnesium helical coil wire. The coil produces 5 to 10 per cent obstruction of the artery and, being thrombogenic in nature, a partial-to-complete occlusion at the wire site usually occurs within 4 to 6 hours. A special double-lumen catheter was passed via the left common carotid artery for wire placement. The coronary arteries were visualized by injection of angio dye through the inner catheter under fluoroscopy. The methodology of wire placement has been described in detail elsewhere. Two to 4 ml of 1:1000 w/v suspension palmitic acid was injected into the coronary artery in 2 to 4 seconds. FFA was injected one-half hour after wire placement in five dogs (Group I), six hours after wire placement in four dogs (Group II) and 2 to 10 days after placement in two dogs (Group III). These three groups represented different stages of coronary occlusion—from acute myocardial hypoxia to 10-day-old myocardial infarct. The observations were made with continuous electrocardiographic monitoring and cardiac silhouette determination under fluoroscopy. Fifteen to 20 seconds following injection of FFA into the coronary artery all the dogs in Group I and Group III and two dogs in Group II showed dilatation of the heart and almost complete loss of contractility under fluoroscopy. The pulse and blood pressure were not obtainable at the end of two minutes. Resuscitative efforts were of no avail and complete mechanical standstill, absence of blood flow, and terminal arrhythmias occurred within three to four minutes. The other two animals in Group II which did not die at first injection of FFA lived for 5 and 10 days, respectively. At this time a repeat coronary arteriography showed 75 to 90 per cent occlusion of the respective coronary arteries at the wire site and injection of 2 ml. of FFA into the coronary artery produced immediate death of the animals with cardiac standstill. The ECG changes observed in the entire study were immediate acute ST segment elevation with NSR 15 to 20 seconds after FFA injection. Later it changed to supraventricular tachycardia or sinus bradycardia ending in sinus arrest with slow idioventricular rhythm. In six of the dogs intraventricular conduction defects and complete heart block were observed 3 to 5 minutes after FFA injection. The terminal arrhythmias were ventricular fibrillations or asystole. These ECG findings are in agreement with earlier experimental and clinical reports. However, as shown, these serious arrhythmias appeared subsequent to myocardial failure.

The clinical implications of these observations, if any, are that during acute myocardial hypoxia or infarction sudden rise in blood FFA level may markedly depress myocardial contractility leading to drop in cardiac output and ending in serious arrhythmias. Recent observations that physiological concentrations of FFA have a marked depressant effect on the perfused rat heart under hypoxic conditions[6] further corroborate our findings and suggest a plausible mechanism.

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Book reviews

ANATOMICAL STUDIES ON THE MOTION OF THE HEART AND BLOOD. By William Harvey M.D. (The Leake Translation) Springfield, Ill., 1970 Charles C Thomas, Publisher 150 pp. Price $4.50.

This translation by Dr Chauncey D Leake is now in the fifth edition. The photographs of Harvey are interesting and well chosen. The contributions of Harvey related to the circulation were historic as   ttested again by this small volume. Leake reviews very well some of the events that transpired around the world in memory of Harvey and his work on the tercentennial of his death in 1657 The preface is an interesting and important recording of medical history The first edition of this small book was published in 1928. It still commands considerable interest. All physicians and students should find the book of interest even though they may not be in the field of the heart and circulation. This is   good book which is highly recommended.

INTENSIVE MEDICAL CARE. By Edward Rubenstein, M.D F.A.C.P New York, 1971 McGraw-Hill Book Company Inc. A Blakiston Publication, 276 pp. Price $6.50.

Rubenstein has developed   small, almost pocket size, paperback volume from his personal notes on the intensive medical care of patients. This is   brief presentation of the management of cardiac arrest, myocardial infarction, shock, arrhythmias, heart block, respiratory failure, renal failure, metabolic crises, and other acute medical emergencies. The presentation is clear Of course, management of patients with any of the medical emergencies is difficult and varies with each patient. Thus, Rubenstein   book can only serve as   source for general principles and dosage of drugs. This is   useful book which is recommended for beginners and nurses as   quick reference only

ENTWICKLUNG IN EXPERIMENTELLE GRUNDLAGEN MODERNER HERZMUSKELPATHOLOGIE. Von Dozent Dr.sc. med. Arno Hecht Jena, 1970 Gustav Fischer Verlag, 386 pp.

This is   very good book on heart muscle pathology The author has included   considerable amount of electron microscopic studies of the ultrastructure of myocardial disease. There are also histochemical presentations to support the histology   nd ultrastructural changes discussed. The illustrations are good   nd the bibliography is extensive. The emphasis on the electron microscopic aspects of myocardial disease is timely Pathologic changes can be extensive before the light microscope can detect significant alterations or indeed, any changes. This book should interest not only pathologists but also cardiologists or anyone who treats heart disease. Those studying the pathophysiology of heart muscle disease will also find this book to be valuable. The introduction of electron microscopy to cardiac pathology has been an important advancement in cardiology

PROGRESS IN RESPIRATION RESEARCH. VOL. 5 PULMONARY CIRCULATION Edited by J Widimsky S. Daum, and H. Herzog. Basel, 1970, S. Karger AG 463 pp. Price $28.80.

This issue, Vol. 5 of Progress in Respiration Research is devoted to the pulmonary circulation. The contents is   summary of an international symposium on pulmonary circulation held in Prague, June 10 to 13 1969 Even though the monograph is two years old it contains important discussions of   portion of the circulation which has received relatively little consideration over the years. Each presentation is short, of conventional nature, and supported by a brief bibliography The respective discussions are, therefore, far from complete. The discussion sections are, as usual, interesting and reflect well the thinking of the contributors to the symposium. Those who are concerned with the lungs and circulation will find this an interesting volume. But like any scientific paper each presentation must be read carefully and adequately evaluated, because the study of the pulmonary circulation is difficult to perform without introducing important experimental variables too often overlooked by investigators.

CARDIOMYOPATHY PULMONARY EMPHYSEMA. Published on behalf of the Directing Committee of the Society by Prof. Dr J R. Ruttner Zurich, Secretary General of the Society Basel, New York, 1970 S. Karger AG White Plains, N Y Albert J Phiebig, Inc., 230 pp. Price $16.30.

This publication of the proceedings of the Tenth International Society of Geographical Pathology held in Jerusalem, Sept. 1 to 4, 1969 consists of four parts introductory lectures, free communications, symposium on pulmonary emphysema, and free communications on general subjects. The many papers are short. Some presentations include only   brief review of a subject with highly selected bibliography all of which in the   uthor s opinion represent the preferable   pproach to the subject. This is what makes these symposia interesting. Unfortunately some of those in attendance are not directly engaged in experimental or clinical studies or the treatment of the problems they discussed and therefore rely

accentuated first heart sound in the presence of rhythmic heart action. This phenomenon is known as the "cannon sound." The term represents a slight exaggeration because the accentuation of the first sound is often only moderate. More than 50 years ago it was recognized that this accentuation appears when the atrial contraction precedes the ventricular contraction by just a few hundredths of a second. Another clinical sign which is very helpful for the diagnosis of complete A-V block is the periodic appearance of large pulsations in the jugular vein when the atria are controlled by sinus rhythm. This phenomenon may also be seen occasionally in ventricular paroxysmal tachycardia. The explanation for these giant waves is obvious. In textbooks and countless articles this phenomenon is called "cannon waves." By no stretch of the imagination can this phenomenon be compared with a cannon, fired or otherwise.

These lines are written as a plea to abandon this somewhat peculiar terminology. Why not simply state that in complete A-V block large waves appear irregularly in the jugular pulse?

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Editorial

Therapeutics of nature—The invisible sutures of spontaneous closure '

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The natural history of disease is a time-honored subject of medical in terest. The history provided by nature, as a source of *diagnostic* and *prognostic* infor mation is an accepted part of medical practice A more novel use of naturally available information stems from experi ments of nature in which diseases provide experimental models not otherwise avail able in human subjects. I would like to comment on still another view of nature s medical capabilities namely therapeutics of nature The idea that nature can act as a *med cal* therapist is not new poly morphonuclear leukocytes mobilize in re sponse to infection biochemically complex host immune responses are provoked by similar stimuli transplacental maternal antigens protect the newborn infant from infection However the idea that nature can act as a *surgeon* seems strange and remote yet such is the case Let us examine the invisible sutures of nature as they apply to the phenomenon of pontaneous clo sure of congen tal cardiac communications.

The notion that ventricular septal de fects decrease in size after birth is a useful poi t of departure. Normal growth rate of the heart is most rapid during the first 2 years of life[1] during this time a ventricu lar septal defect grows less rapidly than the rest of the heart.[2,3] Accordingly there is a tendency for the *relative* size of the defect to diminish during these early years. This trend continues after age 2 but usually at a slower rate. The tendency for ventricular septal defects to decrease in size finds its ultimate expression in com plete spontaneous closure. At times, the communication remains anatomically pat ent but functionally closed with absent or negligible shunt.[7] Two articles that ap peared in 1918 proposed that ventricular septal defects could close spontaneously One was an article by French entitled "The Possibility of a Loud Congenital Heart Murmur Disappearing When a Ch'ld Grows Up The other an article by Weber carried the title Can the Clinical Manifestations of Congenital Heart Disease Disappear with the General Growth and Development of the Patient? [10] How ever it was not until 1958 and 1960 that documented cases of spontaneous closure were first reported. [11] In fact, spontaneous closure is by no means uncommon and has

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entirely on publications in the medical literature which impress them most. The reader of this publication must keep this in mind. Nevertheless, the symposium must have been an interesting one.

CARDIAC AND VASCULAR DISEASES, *Vols. I and II*. By Hadley L. Conn, Jr. and Orville Horwitz, Philadelphia, 1971, Lea & Febiger Publishers. 1878 pp. Price $39.50.

Conn and Horwitz have edited a two-volume textbook on cardiac and vascular diseases. The splitting of the book into two separate volumes of about 900 pages each instead of producing a single almost physically nonmanageable book will be welcomed by the readers. A textbook is written for a purpose. The authors clearly indicate the impossible task of including the entire literature related to cardiovascular diseases in a textbook. They likewise discuss the errors of medical history, a well known fact observed even in a decade of anyone's life. Nevertheless, they fail to indicate what the objective was in this production involving the efforts of many contributors. This reviewer assumes this textbook is for the use of any undergraduate medical students or physicians who are interested in these many important diseases of man. If this is so, then certain aspects of the book need special comment. For example, there is no section or chapter on history taking or the physical or laboratory examinations, but much on pressure volume and other time-course curves, most of these being obtained from the physiologic literature rather than from the clinical literature. Furthermore, the bibliography is highly selected so that the reader must search the literature for more complete coverage of any subject. The chapters are brief and highly physiologic in orientation. Some chapters remind this reader of the handbooks being published by the Federation of American Societies for Experimental Biology whereas others are more clinically oriented. The reader will find a considerable amount of interesting and important information in these chapters but he will often wonder how some presentations relate to the various diseases he encounters in practice. Of course, if he already knows these relationships he will appreciate their value as presented. Such an approach is to be expected when so many chapters are not written by clinicians in active practice. Just how well such a book will be received by critical physiologists and critical clinicians can be determined only with time. This reviewer would consider the textbook interesting as a single source of information. Surely, each subject is not thoroughly presented, as the authors indicate at the outset. Clinicians, however, will find these two volumes to be complex but a source of much information on many aspects of cardiovascular disease. Considerations of treatment are often presented in a general manner rather than in a specific approach to the patient. For example, the treatment of hypertension includes a listing and discussion of many antihypertensive agents with their actions briefly indicated, but how to integrate this in therapeutics rather than merely clinical pharmacology is not made clear for a practicing physician who must give precise instructions to his patient or write orders on a hospital patient chart. Of course, it is well known that one cannot learn the practice of medicine from textbooks only. Regardless of these remarks, many interesting problems related to cardiovascular diseases are included in this textbook. It should be noted that the book is nicely printed and bound.

after birth.[n,n,n] During this period the left to right shunt may be large enough to cause congestive heart failure yet late spontaneous closure can still occur.[n,n,n] Older children or even adults sometimes experience spontaneous closure of a patent ductus, although the incidence in this age group is unknown. In one child the ductus closed between the ages of 5 and 6 years.[n] In another there was a loud rough continuous murmur with a wide pulse pressure at age 5 years between ages 7 and 14 years, the ductus closed spontaneously.[n] Still another patient had a typical continuous murmur at age 12 years with spontaneous closure at age 19.[n] Campbell[n] described an even more impressive case of a 44-year-old man who had a prominent continuous murmur of patent ductus between the ages of 12 and 17. Many years later only a faint continuous murmur was present, suggesting a substantial decrease in ductal size. At age 44 the man was accepted for life insurance since the murmur had vanished completely. It should be emphasized that the foregoing examples represent disappearance of ductus murmurs because of late spontaneous closure and *not* because of abolition of left to right shunts by increased pulmonary vascular resistance. The mechanisms responsible for late spontaneous closure are unknown. On rare occasions, closure of the ductus has followed the healing of bacterial endocarditis[n,n] or has been due to occlusion of the ductus by vegetations[n] or thrombi.[n]

Delayed spontaneous closure of a patent ductus has not been well publicized. Spontaneous closure of *interatrial communications* is even less well known. In this regard let us first look at the foramen ovale. The anatomic arrangements of the foramen and its valve permit right to left flow in utero but no flow after birth. However under certain pathologic conditions a left to right shunt is established across an essentially normal foramen ovale.[n-n] Under these circumstances, a high left atrial pressure causes dilatation of the left atrium which is believed to stretch the margins of the foramen making its ostium incompetent. Theoretically any condition capable of producing a distended high pressure left atrium can result in a left to right shunt across a patent foramen ovale. This variety of left to right interatrial shunt is more likely to develop in infants and young children in whom anatomic closure of the foramen has *not* yet occurred. However even adults occasionally exhibit left to right interatrial shunts because of incompetence of the foramen ovale secondary to dilatation of the left atrium.[n] When the cause of the enlarged high pressure left atrium is removed the left to right shunt disappears.[n] Such a mechanism must be postulated in some patients presumed to have experienced *spontaneous closure* of their atrial septal defects.[n] It is a point of interest however that an occasional left to right shunt spontaneously disappears for no apparent reason.[n-n] It is not always possible to determine whether such left to right shunts were across *true* atrial septal defects or across incompetent foramen ovales.[n] Nevertheless, a number of reports indicate that true ostium secundum atrial septal defects may undergo spontaneous closure in early childhood.[n-n,n] In one such patient, the left to right shunt had been large enough to cause heart failure prior to spontaneous closure.[n] The mechanisms responsible for spontaneous closure of true atrial septal defects have been speculated upon but remain unknown.[n,n] Experimental atrial septal defects in dogs tend to undergo spontaneous closure months[n] or even years[n] later. However the mechanism of closure in the relatively muscular canine atrial septum is likely to differ from that of the less muscular human atrial septum.[n]

Experiments of nature and *therapeutics* of nature have shed much light on human disease and animal biology. There is little doubt that we need only rekindle our powers of observation in order to discover even more examples of the role of nature as experimenter, medical therapist, and surgeon.

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been estimated to occur in 25 to 45 per cent of ventricular septal defects present during the first few months of life[8,12,13] Isolated ventricular septal defects are about three times as frequent in children as in adults a difference that cannot be explained by childhood mortality[13,14] It is likely that spontaneous closure accounts for this difference[13,14] The majority of defects that are destined to close do so in infancy or early childhood often in the first few years of life[12,13] This pattern is understandable since the relative decrease in size of the defect is greatest during these early years. It has also been postulated that the expected *intrauterine* time of ventricular septal closure may not be limited to early fetal life but may sometimes continue through gestation into the postpartum period[16] This hypothesis is believed to account for the relatively large number of isolated ventricular septal defects among premature infants[16] On the other hand spontaneous closure sometimes occurs even in older children[13] or adults[17] and in one instance which was documented between the twenty sixth and thirty third years of life[12] It is reasonable to suppose that the smaller the initial size of the defect the greater the likelihood of spontaneous closure However the tendency to close naturally is not confined to small defects but also applies to those that previously exhibited appreciable left to right shunts with elevated pulmonary arterial pressures[4,8,11,14,18,21]

Spontaneous closure is accomplished by a number of mechanisms namely direct apposition of the margins of the defect ingrowth of fibrous tissue endocardial proliferation adherence of the septal leaflet of the tricuspid valve to the defect or prolapse of an aortic cusp through the defect.[8,13,14,17,22,24] In one patient the defect was closed by a protruding sinus of Valsalva aneurysm[13] It is important to recognize that closure by an adherent tricuspid leaflet need not be accompanied by tricuspid regurgitation[24] Finally there is evidence that the formation of septal aneurysms is sometimes the prelude to late spontaneous closure of small ventricular septal defects[27] It is of further interest that small experimental ventricular septal defects in dogs have a strong tendency to close[25] Finally spontaneous closure has been reported following traumatic ventricular septal defects caused by perforating missiles[29]

Natural closure of the *patent ductus* in early neonatal life is common knowledge The ductus arteriosus in full term infants normally undergoes an initial stage of functional closure followed by a later stage of anatomic closure[30] Functional patency lasts for only a brief period after birth During this period there is at first a bidirectional shunt after which flow becomes left to right and remains so for about 15 hours[30] Following this the shunt disappears altogether or becomes insignificant.[30] At the end of a week the ductus is generally no more than probe patent and by 4 to 8 weeks anatomic closure has usually taken place[31-34] Variations can be expected but the foregoing patterns are those of normal ductal closure

A patent ductus is usually largest at its aortic insertion and may have the shape of a truncated cone this is so because the tendency to close begins at the pulmonary arterial end[35-37] Occasionally the aortic insertion remains open after the pulmonary end has closed and as time goes on an aneurysm forms in the patent portion[38] Patency confined to the pulmonary arterial end of the ductus is exceptional[38]

In 1904 Williams[39] introduced the concept of *delayed* spontaneous closure of the patent ductus arteriosus although his conclusions were not proved He described the natural history in a young child who was believed to have experienced gradual occlusion of the ductus. Thirty five years later Gross[40] postulated that the low incidence of patent ductus in adults as opposed to children was probably due to late closure In 1950 Brown[41] reaffirmed this view stating that there must be spontaneous closure of the ductus arteriosus more often than is generally realized These comments refer to *late* spontaneous closure beyond infancy and *not* to normal closure in the newborn period Observations from a number of sources support the view that a patent ductus arteriosus can undergo late permanent spontaneous closure[42-46] Delayed closure is more likely to occur in premature infants in whom the ductus may remain patent for as long as 4 to 6 months

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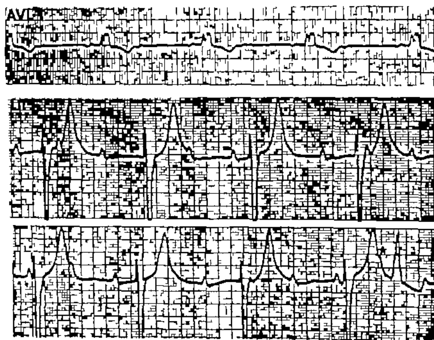


Fig. 1 Rhythm strips obtained just prior to hospitalization. The upper panel (aVL) shows rhythm strip with second-degree A-V block and 2:1 conduction. The lower panel (Lead II) shows segment of long rhythm strip with higher degree of A-V block. The star identifies probable capture beat.

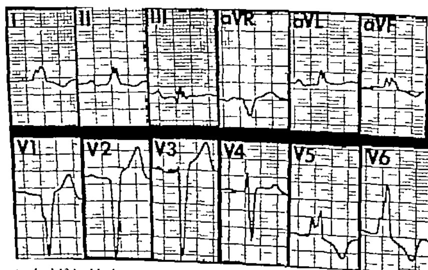


Fig. 2 The standard 12 lead body surface ECG recorded on admission to the hospital.

conduction with periods of 2:1 and 1:1 conduction. Although the information available was suggestive of the presence of bilateral bundle branch block His bundle electrograms were recorded in an effort to more clearly define the site of conduction disturbance. These recordings were accomplished by the method of Scherlag and associates. In addition a 6F bipolar electrode catheter was positioned in the high right atrium to pace or record atrial electrograms. During sinus rhythm with second degree A-V block and 2:1 conduction (Fig. 3) the nonconducted beats were followed by a His bundle potential with the characteristics and timing described in

Clinical communications

Coexisting intra- and subnodal block An unusual abnormality of atrioventricular conduction

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The introduction and popularization of His bundle electrogram recordings has brought new insight into the study of atrioventricular (A V) conduction defects.[1-10] The localization of the site of A V block by recording electrograms from the area of the proximal His bundle has in addition proved to be of both diagnostic and prognostic value.[4,8,11,12]

His bundle recordings in this report document unusual manifestations of A V conduction disturbances not evident from the body surface electrocardiogram (ECG). These studies established the coexistence of intranodal Wenckebach periods and Mobitz Type II block below the proximal His bundle. The recording of His bundle electrograms has challenged many accepted concepts regarding A V block and has brought to light many phenomena previously inapparent from the body surface ECG.

Methods and results

A 73-year-old man without cardiovascular symptoms was found to have electrocardiographic evidence of variable A V block during a routine examination. No abnormalities of A V conduction had previously been noted. Past history revealed no prior evidence of cardiovascular disease.

The physical examination showed a blood pressure of 140/90 mm Hg and a pulse alternating between 36 and 60 per minute. There were no murmurs, no evidence of ventricular enlargement, and no signs of congestive heart failure. No other significant abnormalities were noted.

Rhythm strips obtained just prior to hospitalization demonstrated a transient second-degree A V block with 2:1 conduction (upper panel, Fig. 1) and a higher degree A V block (lower panel, Fig. 1). In a very long rhythm strip, represented by the strip in the lower panel, there appeared to be conduction of atrial impulses only when the R-P interval was 480 msec. (Fig. 1, lower panel). The capture beat closely resembles in morphology a sinus beat as seen in Lead II (Fig. 2). The ECG on admission (Fig. 2) showed sinus rhythm (rate 71 per minute) with complete left bundle branch block (QRS = 0.16 sec.) and a prolonged P-R interval (0.27 sec.).

A 10 hour continuous ECG was recorded by Holter monitor on the second day of hospitalization and showed variable A V

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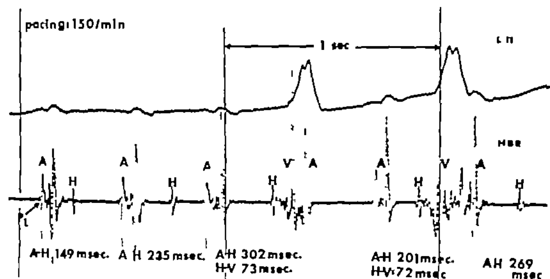


Fig 5 Pacing-induced combined intranodal and subnodal block. Right trial pacing at 150 per minute. P denotes stimulus artifact. See text for discussion.

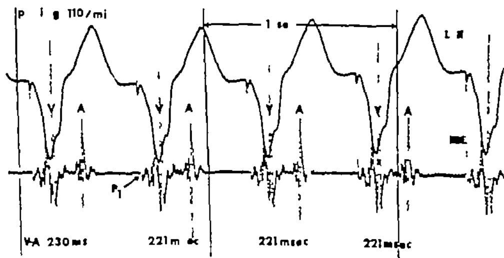


Fig. 6 One-to-one V A conduction. Right ventricular pacing t 110 per minute with P indicating pacing stimulus artifact.

that the first and fourth QRS complexes may be junctional escape beats with the basic rhythm being 3 1 A V conduction. At an atrial pacing rate of 150 per minute (Fig 5) an interesting feature was observed. There was progressive increase in A H time from the first atrial depolarization until block w thin the node after the fourth atrial depolarization (A H times 149 235 and 302 respectively 4.3 conduction) demonstrating an intranodal Wenckebach period and simultaneously Mobitz Type II block below the proximal His bundle. The first A H interval after the dropped His spike has a prolonged A H time of 201 msec. This prolongation beyond the expected minimal A H time of 149 msec. (first A H time) suggests that there was partial penetration of the A V junction (concealed A H conduction) producing an unexpectedly long A-H time. Endocardial pacing at the apex of the right ventricle showed 1 1 V A conduction at a pacing rate of 110 per minute (Fig 6) with V A conduction time being 221 and 230 msec. At a rate of 130 per minute, retrograde

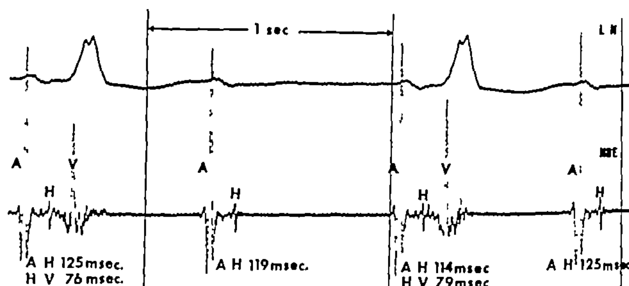


Fig 3 His bundle electrogram recorded during spontaneous 2 1 A V conduction. The upper strip is a Lead II ECG The lower strip is the His bundle electrogram. Low right atrial electrogram, His bundle electrogram, and ventricular electrogram are labeled A, H and V respectively The A H times and H V times, in milliseconds, are shown below each group of complexes. A one-second time calibration is shown at the top of the figure. On alternate beats conduction is blocked below the level of the proximal His bundle.

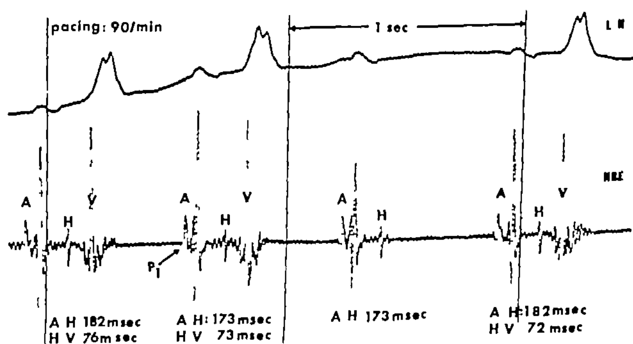


Fig 4 Pacing induced 3.2 A V conduction. Right atrial pacing at a rate of 90 per minute. *P* denotes the stimulus artifact. The third atrial beat was blocked below the proximal His bundle.

previous reports.[5,6] This was evidence of Mobitz Type II A V block and hence of subnodal block of conduction The HV time of the conducted beats was prolonged (76 to 79 msec normal 35 to 45 msec) and indicated delay in conduction distal to the proximal His bundle

Confirmatory evidence of the presence of Type II A V block was obtained by atrial pacing at a rate of 90 per minute At this rate 3.2 A V conduction was observed with every third atrial beat being blocked below the level of the proximal His bundle (Fig 4) Prolonged A H times (173 to 183 msec.) and H V times (72 to 76 msec) were noted The variation in A H time noted in this figure may represent the effect of changes in latency (stimulus to atrial depolarization time) and changes in autonomic tone. However it is possible

heart and pharmacologic interventions. Furthermore its behavior does correlate with the widely accepted electrophysiologic properties of the conduction tissue of the heart studied in the experimental animal.[19-4]

Recording His bundle electrograms has also been used to study A V block in man.[1-4] The recordings in this report of the His bundle potential during Wenckebach phenomenon as well as in the Mobitz Type II block are consistent with the above observations.

The presence of Wenckebach phenomenon or Mobitz Type I A V block has been considered characteristic of intranodal lesions, whereas Mobitz Type II block is regarded as an exclusive feature of subnodal lesions. Friedberg and colleagues,[17] Rosenbaum and colleagues[1] and Narula and colleagues[1] offered evidence that challenged these criteria with reports of Wenckebach phenomenon in the bundle branches and His bundle records showing progressive prolongation of the H V interval until a dropped beat occurs. Furthermore, objective evidence of combined lesions at the nodal and subnodal level had not been available from the surface ECG s. Based on His bundle electrograms Narula and associates[1] and Schuilenburg and Durrer have reported cases with evidence suggestive of impaired A V conduction with block at two levels.

It is indeed unusual however to have retrograde conduction in the presence of advanced A V block. Previous studies in patients with advanced A V block have shown unimpaired retrograde conduction in only 12 of 58 cases.[19, 22] This patient had 1 1 retrograde conduction during ventricular pacing at 110 per minute with a V A conduction time of 221 msec. This time was within the range (160 to 280 msec.) for retrograde conduction in patients with normal A V conduction.[19] However the presence of retrograde Wenckebach periods at a paced ventricular rate of 130 per minute suggests that there may have been some abnormality of retrograde conduction as well.

In this patient standard ECG the presence of 2 1 A V block was considered evidence of Mobitz Type II block only because subsequent periods of changing A V conduction with a fixed P R interval were demonstrated (Figs 1 3 and 4).[11, 22] In addition when the patient was in sinus rhythm left bundle branch block with a prolonged P R interval was present (Fig 1). According to Lepeschkin[23] this supports the diagnosis of bilateral bundle branch block. Extensive pathologic studies by Lenègre[24] have documented the findings associated with bilateral bundle branch block. Among those, extensive fibrosis encroaching upon the bundle branches without involvement of the coronary vasculature was a frequent cause of bilateral bundle branch block.[24] The demonstration by His bundle electrograms of block below the proximal His bundle seen both during sinus rhythm and with atrial pacing offered confirmatory evidence for the presence of this entity.[12] The absence of clinical manifestations of coronary artery disease, hypertension or aortic valvular disease in this case points toward the sclerosis of the cardiac skeleton as a possible pathologic explanation of the conduction disturbances.

Despite absence of symptoms, a permanent demand pacemaker was implanted in this patient. This therapeutic intervention was undertaken because of the evidence from His bundle electrograms, suggestive of bilateral bundle branch block coupled with the knowledge of the reported frequent occurrence of complete heart block in patients with Mobitz Type II A V block.[21]

Summary

The presence of A V block occurring at two levels of the conducting system was demonstrated in an asymptomatic patient by means of the His bundle recordings. During sinus rhythm first degree A V block with complete left bundle branch block was noted suggesting the presence of bilateral bundle branch block. His bundle recordings demonstrated the coexistence of intranodal (Wenckebach periods, Mobitz Type I) and subnodal (Mobitz Type II) block. The evidence of block below the proximal His bundle offered confirmatory evidence of bilateral bundle branch block. In spite of the abnormal antegrade conduction there was 1 1 V A conduction during

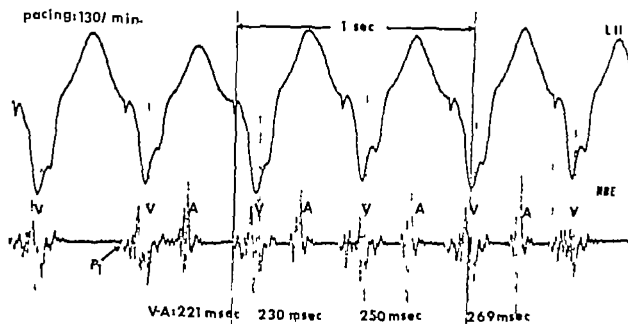


Fig. 7. Retrograde Wenckebach. Right ventricular pacing at 130 per minute with P indicating the pacing stimulus artifact. There is progressive prolongation of the V-A conduction time after first beat (P_1) of the group (221, 230, 250, and 269 msec., respectively, 5:4 conduction) until an atrial beat is blocked.



Fig. 8. Rhythm strip after pacemaker implantation. Transvenous pacemaker catheter located in the apex of the right ventricle. Beats marked with the star are apparent captures.

Wenckebach periods were produced with progressive prolongation of the ventricular to retrograde P potentials until a dropped P wave occurred (Fig. 7). At the end of the procedure a 6F bipolar pacing catheter was positioned in the apex of the RV and connected to a demand pacemaker set at 50 per minute. A rhythm strip from Lead V3R (Fig. 8) shows the pacemaker induced ventricular complexes interrupted by P waves which apparently were conducted only when occurring just after the summit of the T wave (QRS-P interval 360 msec.) and again were suggestive of supernormal conduction (see Fig. 1).

Discussion

Giraud and colleagues[1] in 1960 published a record of His bundle potentials obtained during cardiac catheterization in a patient with the trilogy of Fallot. This report was followed in 1967 by a study by Watson and associates[2] who recorded potentials from the His bundle in a patient with Ebstein's anomaly of the tricuspid valve. The records obtained by these authors were consistent in morphology, duration, and timing with the records experimentally obtained from the His bundle by Alanis and associates,[13] Scher and associates,[14,15] and Hoffman and associates.[16] A technique for ventricular pacing as well as recording of electrical activity from the His bundle was described by Scherlag and associates[3] in 1967 and later applied to routine recording of His bundle activity in man during right heart catheterization.[4,5] The His bundle potential recorded by these techniques appears as a diphasic or triphasic wave with a duration of 15 to 20 msec. occurring between the atrial and ventricular electrograms. The validity of the recorded deflection as a true His bundle potential has been intensively analyzed with electrical stimulation of the

Thrombosis of the inferior vena cava following balloon septostomy in transposition of the great arteries

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Following initial palliation of infants with transposition of the great arteries (TGA) by balloon atrial septostomy (BAS) a corrective operation (Mustard procedure)[1] was previously performed electively on patients between two and three years of age at the Royal Alexandra Hospital for Children. This paper describes an unexpected complication of BAS which was discovered at the time of preoperative study thrombosis of the inferior vena cava (IVC)

Materials and methods

Eleven patients with TGA who had BAS as neonates have undergone recatheterization either as a preliminary to elective repair (eight patients) or because of unsatisfactory progress (five patients) Two of the patients are included in both groups.

BAS had been performed in six cases using the right femoral vein (which was subsequently repaired) In six infants the right saphenous vein near the saphenofemoral junction was used. In one case both approaches were employed at two different times. In all cases an Edwards No 6 double-lumen balloon catheter* was used

At restudy the initial approach was to perform a cutdown on the left long saphenous vein or on a right antecubital vein if previous cutdown had been performed in both femoral regions.

The venous abnormality was demonstrated in two cases by hand injection of contrast medium (1 to 2 ml of 60 per cent Urografin) into the left iliac vein when the catheter could not be advanced into the IVC. In the third case the IVC was catheterized retrogradely from the right atrium and the block was demonstrated to be below the level of the renal veins.

Case reports

Case 1 D H., 3 740 gram female infant, presented with increasing cyanosis since birth. Cardiac catheterization established diagnosis of TGA with small ventricular septal defect. BAS was performed t 24 days of age, the catheter being passed from the right femoral vein. Some difficulty was experienced in repairing the vein, but cyanosis and a

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right ventricular pacing at 110 per minute. With more rapid (130 per minute) ventricular pacing retrograde Wenckebach periods were observed suggesting that there was in addition possible impairment in retrograde conduction This report serves to demonstrate (1) the limitations of the body surface ECG in the assessment of A V conduction and (2) that His bundle electrograms make it possible to detect the presence of coincidental lesions at two levels of the A V conducting system

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Thrombosis of the inferior vena cava following balloon septostomy in transposition of the great arteries

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The venous abnormality was demonstrated in two cases by hand injection of contrast medium (1 to 2 ml. of 60 per cent Urografin) into the left iliac vein when the catheter could not be advanced into the IVC In the third case the IVC was catheterized retrogradely from the right atrium and the block was demonstrated to be below the level of the renal veins.

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slight swelling of the right leg disappeared within a few days and the patient progress wa satisfactory without evidence of venous obstruction. She was studied at the age of two years and nine months to assess her suitab lity for corrective operation. When a catheter could not be passed from the left long saphenous vein past the iliac vein i jection of con trast medium revealed a venous block and a leash of anastomotic vessels draining into the IVC at about the level of the renal veins. There wa no difficulty with cannulation of the IVC from the right atrium for cardiopulmonary bypass.

Case 2 M M a 3,500 gram female infant presented with cyanosis at two days of age At that time the diagnosis of TGA was confirmed by card ac catheterization and BAS wa performed from the right femoral vein. Infect on of the cutdown wound occurred but healed completely without persistent signs of venous obstruction in the leg At four months of age a repe t BAS wa attempted from the left femoral vein but the catheter could not be passed into the IVC and a Blalock Hanlon operation was performed At the ge of two year and eight month cardiac catheterization was performed prior to corrective urgery Thrombosis of the IVC below the level of the renal veins was demonstr ted Again there was no difficulty in cannulating the IVC for cardiopulmonary bypass.

Case 3 I Mc. a 2 830 gram female infant presented with cyanosi at two days of age Cardiac catheterization estal lished the diagnosis of TGA and BAS was performed from the right long saphenous vein. Her initi l good response was not main tained and BAS w s repeated three weeks later using the right femoral vein there was little im provement in her condition, however At four months of age a further catheterization was attempted. However approach from the left long saphenous vein revealed a thrombosed IVC. The patient subsequently died following a Blalock Hanlon opera tion. At autopsy the atrial septum was thick and muscular in the usual position of the valve of the fossa ovalis, accounting for the failure of the balloon septostomy The IVC and both renal veins were thrombosed but the kidneys appeared normal on both macroscopic and microscopic examination.

Discussion

In each of these three children the balloon catheter was introduced into the femoral vein this same method was used routinely in our early cases. Later we found that BAS could almost always be performed using the saphenous vein if this was carefully dissected to its junction with the femoral vein This approach is simpler quicker and results in less blood loss. In addition the femoral vein is spared and there is less postoperative venous stasis in the leg No instance of IVC thrombosis was found at recatheterization of six children in whom the long saphenous vein had been used for insertion of the balloon catheter

Furthermore the IVC thrombosis which occurred in Case 3 was not present between the first BAS performed by means of the saphenous vein and the second BAS done through the femoral vein

Nevertheless the site of catheter entry does not entirely explain the complication. Four infants in this series in whom the femoral vein was used for initial catheter insertion have not had this complication at restudy and we can find reference to only two other cases in the literature[3] although there may be many unreported cases.

In our first case hemostasis was difficult to achieve and the more than usual tissue trauma may have caused excessive local release of clotting factors. In the second infant the cutdown site became infected In the third severe cardiac failure with sluggish circulation might have predisposed to venous thrombosis

The catheter used for BAS is large and stiff and the balloon when collapsed is rough and probably causes endothelial damage We have not observed IVC throm bosis following neonatal cardiac catheter ization using standard No 5 catheters, but these catheters are almost invariably in troduced into the saphenous vein We may speculate whether our practice of repairing rather than ligating the femoral vein en courages the spread of thrombosis from the catheter entry site It is also interesting to speculate as to when the thrombosis occurs and whether it occurs massively or by stages.

None of the children reported had a history suggesting acute caval thrombosis. Proteinuria did not occur even in Case 3 where renal vein thrombosis was found Absence of clinical and pathological evi dence of distant embolization supports the concept of a slowly developing thrombosis. In an older age group leg and pelvic vein thrombosis is not infrequently followed by significant pulmonary embolism[4]

Though thrombosis of the IVC in these children appears to have been of no clinical significance because of the sparing of the renal veins or the development of adequate collateral circulation venous insufficiency of the lower limbs may develop later

This complication is of practical impor tance in the reinvestigation of patients with TGA and BAS prior to their undergoing

Table I. State of IVC at restudy

Site of initial cutdown	*Thrombosed*	*Patent IVC*	*Total*
Femoral vein	3	3	6
Saphenous vein	0	6	6

corrective surgery as approach from a leg vein may sometimes be impossible (Table I). Although we were initially concerned that probing of the atrial septal defect and catheterization of the left ventricle and pulmonary artery might be more difficult from the antecubital vein, this has been achieved by means of the "floppy wire technique"[5] in all cases attempted just as easily as with the saphenous vein approach.

In the two cases with IVC thrombosis reported by Zamora and associates, no details of the initial BAS are given and although additional femoral vein cannulation was necessary at their Mustard repair, this was not so in the two cases which came to corrective surgery.

In view of the possibility of multiple cardiac catheterizations in cases of TGA, including pre- and postoperative assessment of Mustard repair, an effort should be made to preserve as many veins as possible. Consequently, the saphenous rather than the femoral vein should be used whenever possible to perform the initial BAS.

Summary

Three cases of thrombosis of the inferior vena cava following balloon atrial septostomy for transposition of the great arteries are described. Possible factors in the pathogenesis are discussed and attention is drawn to the silent presentation and practical importance of this complication.

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Dicrotism in heart disease

Correlations with cardiomyopathy, pericardial tamponade, youth, tachycardia, and normotension

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In June 1963 one of us (W. R. M.) palpated a double impulse over the brachial artery of a patient with alcoholic cardiomyopathy. A direct arterial pressure tracing demonstrated a dicrotic pulse, i.e., the dicrotic notch was low and the wave following it was high. It was assumed that the palpating fingers had sensed both the systolic and the dicrotic waves.

A few months later another case of congestive cardiomyopathy was found to have a double brachial artery impulse. In this instance the direct recording initially revealed a wave form without unusual features, but when the artery was digitally occluded at the hub of the needle, the pulse contour immediately became dicrotic. It was concluded that our customary use of three fingers when palpating the pulse had resulted in the index finger becoming the sensing mechanism; at the same time the middle and ring fingers exerted occlusive pressure distally.

As more instances of dicrotic brachial artery pulses came to our attention, it became apparent that we were making observations that had not previously been reported. Accordingly, it was decided to study the direct brachial pulse in a series of normal subjects and in patients with various categories of heart disease. The observations made during the study are the subject of this report.

Materials and methods

The 28 normal subjects were either medical students or individuals in the hospital for minor medical or surgical reasons. Nineteen were Caucasian and 9 were Negro. The patient study consisted of two parts. One part was a review of the records of 131 patients with regular heart rhythm who had undergone cardiac catheterization in this laboratory between October 1960 and December 1965. Sixty-one of these patients had brachial artery tracings, and 70 had radial artery tracings. The other part of the study was prospective and was made up of the brachial artery pressure tracings of 166 patients with cardiac disease who came to our attention from June 1966 to April 1970. As a separate analysis of

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Table I Pulse contour

Diagnostic categories	Age (years)	Without distal occlusion of brachial artery						With distal occlusion of brachial artery					
		N	Age			Dicrotic		N	Age			Dicrotic	
			Range	Median	Mean	Fully	Border-line		Range	Median	Mean	Fully	Border line
Normal subjects	<45	17	22-44	25	30	0	0	17	23-41	25	30	1 (6%)	1 (6%)
	>44	11	46-57	48	49	0	0	11	46-57	48	49	0	0
Cardiomyopathy	<45	42	19-44	35	33	16 (38%)	2 (5%)	18	19-43	40	35	8 (44%)	4 (22%)
	>44	34	45-75	51	53	1 (3%)	2 (6%)	22	45-73	52	55	7 (32%)	6 (27%)
Atherosclerotic heart disease	<45	4	31-43	38	37	0	0	4	31-43	38	37	0	1 (25%)
	>44	27	45-75	62	58	1 (4%)	0	23	45-73	56	56	5 (22%)	1 (4%)
Hypertensive heart disease	<45	7	34-44	40	38	0	0	6	34-44	41	39	0	0
	>44	13	45-61	50	51	0	0	12	45-61	50	51	0	1 (8%)
Mitral stenosis	<45	11	33-44	40	38	0	3 (27%)	3	38-43	40	40	0	0
	>44	10	46-57	50	50	0	0	7	47-57	51	51	0	1 (17%)
Mitral insufficiency	<45	1	37	37	37	0	0	—	—	—	—	—	—
	>44	15	46-82	51	51	0	0	9	46-59	50	52	0	0
Aortic stenosis	<45	6	36-43	42	41	0	1 (17%)	2	41-43			0	0
	>44	12	46-74	58	58	0	0	6	45-74	65	66	0	0
Aortic insufficiency	<45	17	28-44	39	38	0	0	8	33-44	41	42	0	0
	>44	13	45-70	55	54	0	0	7	50-70	54	57	0	0
Mixed valvular	<45	10	33-43	40	39	0	0	2	41-43			0	0
	>44	4	45-58	47	49	0	0	1	46	46	46	0	0
Miscellaneous	<45	28	27-44	35	38	0	0	8	27-44	38	38	0	2 (25%)
	>44	36	45-77	51	55	0	0	12	45-77	50	55	1 (8%)	0

these two groups gave similar results, the findings were combined for greater simplicity of presentation.

The diagnostic categories with the number of younger and older patients in each are included in a listing of data in Table I. Except for one patient with idiopathic hypertrophy whose symptoms were limited to a decrease in exercise tolerance, palpitations, and episodes of syncope, all cases of cardiomyopathy were of the congestive type. The patients were either in congestive failure at the time of the study or convalescent therefrom. A majority were Negro and alcoholic. The patients with hypertensive heart disease were similarly in congestive failure or were recovering from it. Patients with arteriosclerotic heart disease were either in clinical congestive failure, recovering from it, or were shown by angiography to have markedly decreased centripetal movements of the left ventricular wall during systole. The diagnosis was made by history, electrocardiogram (ECG), and in 8 instances, by coronary angiography. The degree of cardiac difficulty of the 99 patients with valvular heart disease ranged from nonexistent to that of marked congestive failure. Forty-four of the 81 who were catheterized had oxygen arteriovenous differences greater than 5.0 volumes per cent. Forty-eight of the 64 patients in the miscellaneous group were catheterized and 17 had oxygen arteriovenous differences greater than 5.0 volumes per cent.

The pulses were measured by a P23Gb

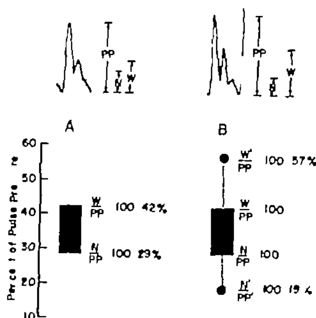


Fig 1 Manner of presentation of the dicrotic wave pressure (W) and the dicrotic notch pressure (N) as a percentage of the pulse pressure (PP) in bar graph form. A Without distal occlusion of the artery B With distal occlusion of the artery. See text for further explanation.

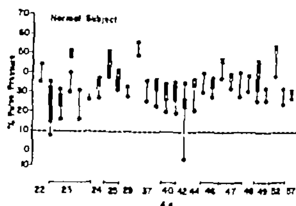


Fig 2 Twenty-eight normal subjects. One becomes fully dicrotic with the distal pressure on the brachial artery. See Fig 1 and text for explanation of the manner of presentation.

Statham strain gauge transducer connected through two three way stopcocks to a No 20 Riley needle and the resulting pressure waves were registered by an Electronics for Medicine DR8 recorder. The stroke volume index (SV_I) of those patients who were catheterized was estimated by dividing the resting cardiac index (direct Fick method) by the heart rate.

The pulse wave chosen for measurement was representative of the remaining pulses on the individual tracing. Pressure measurements were made from the zero base line to the end of diastole, the peak of systole, the nadir of the dicrotic notch and the peak of the dicrotic wave. The pulse pressure (PP), the dicrotic notch pressure minus the end-diastolic pressure (N), the dicrotic wave pressure minus the end diastolic pressure (W), and the dicrotic wave pressure minus the dicrotic notch pressure (W−N) were derived from the above measurements. The latter three pressures were then portrayed as percentages of the pulse pressure in modified bar graph form as explained in Fig 1. The top of the bar indicates the peak dicrotic wave pressure minus the end-diastolic pressure and the bottom of the bar represents the dicrotic notch pressure minus the end-diastolic pressure both as percentages of the pulse pressure, i.e.

$$\frac{W \times 100}{PP} \text{ and } \frac{N \times 100}{PP}$$

The length of the bar then becomes the height of the dicrotic wave from the notch as a percentage of the pulse pressure, i.e.

$$\frac{(W-N) \times 100}{PP}$$

In this way one immediately perceives quantitatively those pressure relationships which characterize the dicrotic pulse. The same parameters with digital occlusion of the artery just distal to the indwelling needle, i.e.

$$\frac{W' \times 100}{PP'}, \frac{N' \times 100}{PP'} \text{ and } \frac{(W'-N') \times 100}{PP'}$$

are shown as linear extensions of the bar ending in closed circles. The occlusive maneuver was done only in the prospective patients. Fig 2 gives the data presented in this manner for the normal subjects.

Probability values were obtained from the Student t test.

Results

Unless otherwise stated, the presentation of data refers to the pulse obtained without occlusion of the brachial artery distal to the indwelling needle. As previously indicated, however, bar graphs of the patients in the prospective study will show the results without as well as with distal occlusion.

Definitions. All pulses in this study are shown in a scatter graph (Fig 3) where

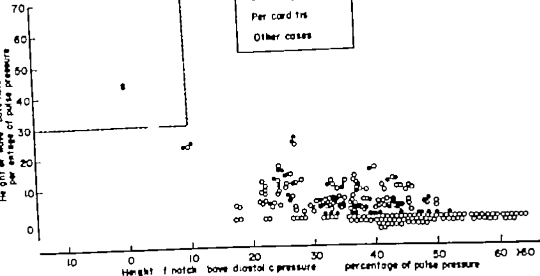


Fig. 3. Scatter graph plotting dicrotic wave (W−N) against the dicrotic notch (both as percentages of the pulse pressure) for each individual in the study. The enclosed group in the upper left corner are considered fully dicrotic.

$\frac{W-N}{PP} \times 100$ on the ordinate is plotted against $\frac{N}{PP} \times 100$ on the abscissa. The pulses of 17 subjects with cardiomyopathy 3 with pericardial tamponade and 1 with atherosclerotic heart disease form a group in the left upper portion of the graph which is more or less separate from the remaining ones. Each has a notch which is less than 10 per cent of the pulse pressure and a wave (W−N) which is 30 per cent or more of the pulse pressure. A visual projection of the dashed lines enclosing this group shows only 7 of the remaining pulses having notches either of this depth (4) or waves of this height (3). Wiggers quotes Otto Frank to the effect that true dicrotism can be said to exist only when the preceding dicrotic dip very nearly reaches the base line in a smooth curve and then rises again to the usual height. In the present study the height of the wave (W) above the diastolic pressure was an average of 47 per cent of the pulse pressure for the 21 pulses in the above group and 43 per cent for the remainder of the pulses. Lewis[3] stated that "a dicrotic pulse may then be defined as one in which the pressures represented by the dicrotic curve bear a certain minimal relationship to the pressures represented by the primary wave. He recognized the difficulty in fixing a standard of dicrotism and did not set any values on these minimal relationships but did include a schematic drawing of a dicrotic pulse with the notch at the level of the diastolic pressure and the dicrotic wave 30 per cent of the pulse pressure.

Because of these considerations it was decided that for the purposes of this study a fully dicrotic pulse would be defined as one whose notch is less than 10 per cent of the pulse pressure and whose wave (W−N) is 30 per cent or more of the pulse pressure. It was also decided to include an arbitrary definition of a borderline dicrotic pulse as all other pulses whose dicrotic notch does not exceed 20 per cent of the pulse pressure and whose wave (W−N) is not lower than 20 per cent of the pulse pressure. Writers of a century ago used three terms to describe the various degrees of dicrotism. A pulse was hypodicrotous when the notch failed to reach the level of the diastolic pressure, dicrotous when it did, and hyperdicrotous when it fell below the diastolic pressure. It is perplexing that this classification did not include standards for the height of the wave.

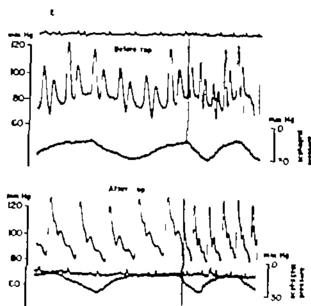


Fig 4 Radial artery pressure tracing immediately before and after removal of 1,500 c.c. of serosanguinous fluid in a case of metastatic carcinoma of the pericardium The dicrotism disappears with the removal of the fluid Time lines 0.04 second

Incidence according to diagnostic categories Table I gives the number and percentage of dicrotic pulses in the younger and older age groups of the various diagnostic categories. Not included in the table were 7 cases of pericardial disease Four patients (aged 2? 33 37 and 48) had pericardial tamponade and all were markedly dicrotic (Fig 4) except 1 aged 33 who was dicrotic only during inspiration The 48 year-old patient also had a diagnosis of cardiomyopathy prior to the onset of purulent pericarditis. Another patient aged 44 with pericardial effusion but no tamponade, developed a dicrotic pulse only with distal occlusion of the artery Two cases of constrictive pericarditis aged 50 and 68 did not have dicrotic pulses (the distal occlusive maneuver was not done in these patients)

Influence of age As shown in Table I a markedly dicrotic pulse in this study was found for the most part in patients below the age of 45 Fig 5 shows in bar graph form the pertinent parameters of each cardiomyopathy pulse in relation to the age of the patient. The clustering of the markedly dicrotic pulses in the younger age group, especially that between 28 and 38 years, is striking In contrast, dicrotism occurring only with distal occlusion of the artery does not appear to have any definite relation to age. The fractional number becoming fully dicrotic with distal occlusion in the various age groups is as follows (borderline dicrotism in parentheses)

	< 40 years	
Cardiomyopathy	5/8	(2/8)
Arteriosclerotic heart disease	0/3	(1/3)
	40-49 years	
Cardiomyopathy	6/17	(4/17)
Arteriosclerotic heart disease	1/7	(0/7)
	50-59 years	
Cardiomyopathy	4/11	(3/11)
Arteriosclerotic heart disease	3/9	(0/9)
	> 59 years	
Cardiomyopathy	0/4	(1/4)
Arteriosclerotic heart disease	1/9	(1/9)

Influence of heart rate Fig 6 illustrates the relation of dicrotism to heart rate. Here again there is marked clustering of the dicrotic pulses, most of them occurring at rates of 94 beats per minute or above. When the group below the age of 40 is considered separately it is found that only 1 out of 11 with heart rates of less than 94 was dicrotic and only 2 of 14 with rates of 94 or above were not dicrotic With distal pressure both of the exceptions became fully dicrotic. Dicrotism that occurred only with distal occlusive pressure was similarly related to rate (borderline dicrotism in parentheses)

	< 90 beats per minute	*90 beats per minute or more*
Cardiomyopathy	1/17 (4/17)	14/23 (6/23)
Arteriosclerotic heart disease	0/15 (1/15)	5/13 (1/13)

Influence of blood pressure There were only 2 patients in the combined cardiomyopathy hypertensive and atherosclerotic groups who were below the age of 40 who had a rate of 94 beats per minute or more and who also had a systolic pressure above 134 mm Hg Evaluation of any relationship that the blood pressure might have to dicrotism was not possible under these circumstances This aspect of the study was therefore restricted to those patients of any age who had a heart rate of 90 beats per minute or more and whose

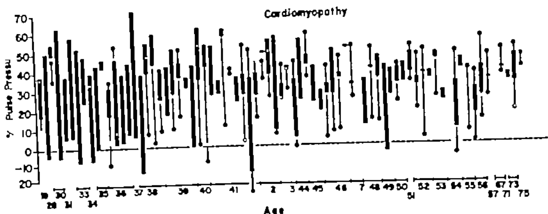


Fig. 5 Pulses of 76 patients with cardiomyopathy arranged according to age. Note clustering of dicrotic pulses below the age of 38. See Fig 1 and text for explanations of the manner of presentation.

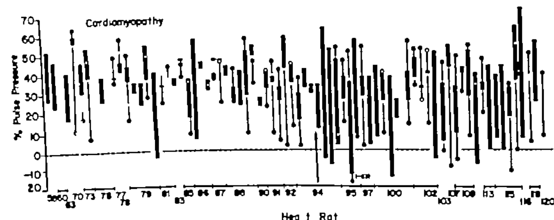


Fig. 6. Pulses of 76 patients with cardiomyopathy arranged according to heart rate. With the exception of 2, all 17 dicrotic pulses have heart rates of 94 or above. See Fig 1 and text for explanations of the manner of presentation.

dicrotism appeared only with distal pressure (borderline dicrotism in parentheses)

Systolic pressure	>134 mm. Hg	<135 mm. Hg
Cardiomyopathy	0/7 (4/7)	14/16 (2/16)
Hypertensive heart disease	0/7 (1/7)	—
Atherosclerotic heart disease	0/1 (0/1)	5/13 (1/13)

Diastolic pressure	>90 mm. Hg	<90 mm. Hg
Cardiomyopathy	0/4 (2/4)	14/19 (4/19)
Hypertensive heart disease	0/6 (1/6)	0/1 (0/1)
Atherosclerotic heart disease	0/1 (0/1)	5/13 (1/13)

Although these figures suggest that a fully dicrotic pulse is not to be expected when the blood pressure exceeds 134/90 mm Hg. It is to be noted that, as an exception 1 of the 21 patients with a fully dicrotic pulse without distal pressure had a pressure exceeding this level (154/91 mm. Hg) Nevertheless, the over-all observations suggest that if the heart rate is 90 beats per minute or more and the blood pressure does not exceed 134/90 mm. Hg over 90 per cent of patients with cardiomyopathy in congestive failure will have a fully dicrotic brachial pulse provided the occlusive maneuver is used if dicrotism is not present otherwise This study leaves unanswered why in the presence of a pulse rate exceeding 89 beats per minute and a blood pressure less than 135/90 mm. Hg patients with atherosclerotic heart disease were less likely than patients with cardiomyopathy to have a dicrotic pulse with distal pressure Three of the 8 patients with

Table II

Patient	*Age*	*W – N**	*N*	*Rate*	*SVI*	*A V $O_2\Delta$*	*LAP*	*LVEDP*	*SVR*	*SP*	*DP*	*PP*
Cardiomyopathy (<40 yr) not fully dicrotic												
D C.	19	21	17	85	37	6 8	24	23	1235	118	70	48
G B	33	24	24	60	32	6 1	9	7	1401	130	72	58
J L.	35	4	43	86	25	7 0	—	13	1380	102	66	36
O W	39	5	31	79	31	5 8	—	—	1922	131	80	51
O C.	39	25	17	63	40	5 4	8	6	1480	128	80	48
C S.	39	11	20	81	21	7 7	13	27	2053	99	62	37
Mean	34	—	—	76	31	6 5	14	15	1579	118	72	46
Cardiomyopathy fully dicrotic												
A W	31	53	6	86	21	7 4	22	33	2061	126	82	44
N C	31	32	6	115	33	4 8	26	27	1134	127	83	44
L O	33	59	−7	94	18	7 3	21	27	1906	111	74	37
K T	36	35	3	100	29	6 9	19	22	1009	113	74	39
J L.	36	37	7	100	33	4 6	6	10	1215	125	67	58
W H	36	43	0	115	22	6 5	17	17	1108	98	50	48
J W	38	50	−13	100	33	6 3	22	17	1134	108	70	38
M J	42	45	9	95	11	13 1	28	—	2786	89	66	23
S H	49	44	−4	79	21	8 6	25	—	1729	153	95	58
Mean	37	—	—	98	25	7 3	21	22	1565	117	73	43
t	0 72	—	—	3 7	1 65	0 92	1 68	1 29	0 05	0 11	0 32	0 59
p		—	—	<0 01								

Abbreviations W – N dicrotic wave minus dicrotic notch as percentage of the pulse pressure N dicrotic notch as percentage of the pulse pressure SV stroke volume index; A V $O_2\Delta$ arteriovenous oxygen difference LAP left atrial pressure LVEDP left ventricular end-diastolic pressure; SVR, systemic vascular resistance in dynes sec.cm.$^{-5}$; SP systolic pressure DP diastolic pressure and PP pulse pressure.

atherosclerotic heart disease who did not have a dicrotic pulse were shown to have large poorly contracting ventricles with high end-diastolic pressures and 1 of them had an oxygen arteriovenous difference of 6 4 volumes per cent and a SV_I of 19

Six of the 8 borderline dicrotic pulses listed in Table I were those of patients below the age of 40 and none of these 6 had rates exceeding 88 beats per minute The remaining 2 aged 48 and 54 had rates of 94 and 109 respectively One a patient with mitral stenosis had a systolic pressure exceeding 134 mm Hg The pattern of factors described for full dicrotism appears to have less importance for the borderline classification

Hemodynamics Catheterization data were available on 34 of the patients with cardiomyopathy whose pulse characteristics are portrayed in Fig 6 In an attempt to obtain a greater insight into the reason for the higher frequency of dicrotism in the presence of tachycardia the hemodynamic information obtained on the 13 catheterized cases (data to the left of the arrow heart rate of 94 beats per minute or below) was compared with the data from the 21 cases to the right of the arrow (heart rate of 94 beats per minute or above) Although the differences in the means and medians of the stroke volume indices oxygen arteriovenous differences, and the left ventricular filling pressures all suggested that the patients with tachycardia as a group were in a greater degree of congestive failure the difference in the means of the stroke volume indices was the only parameter having a p value < 0 1 There was practically no difference in the means of the systemic vascular resistances of the two groups. The mean blood pressure of the group with tachycardia was 120/79 mm Hg (pulse pressure 41) as compared with 131/75 mm Hg (pulse pressure 57) for those without tachycardia, but only the difference in pulse pressures was statistically significant (p < 0 01)

Table II presents the individual hemodynamic data on patients with cardio-

myopathy under the age of 40 who were not fully dicrotic as compared with those patients with cardiomyopathy of any age who were fully dicrotic. The data suggest that those with a dicrotic pulse were as a group in more severe heart failure but statistical significance was reached only for the heart rate ($p < 0.01$) It should be noted that 2 of the patients with dicrotism had normal oxygen arteriovenous differences at rest both however had other evidences of failure either at rest or during exercise.

Forty-one of the pressure tracings were those of patients below the age of 40 who had valvular (23) or miscellaneous types (18) of heart disease other than cardiomyopathy atherosclerotic heart disease or pericardial effusion Four all with heart rates below 89 beats per minute, barely met criteria for borderline dicrotism but none were fully dicrotic. Seven of these 41 patients had pulse rates of 94 beats per minute or more and 15 had an oxygen arteriovenous difference exceeding 5 0 volumes per cent, but only 3 had both Included in this group was a 37 year-old patient with primary pulmonary hypertension who had a heart rate of 81 beats per minute and a SVI of 19

In seven instances dicrotism that was present initially was not found on a subsequent examination (Fig 7) The interval for these observations varied from 3 days to 4 years. With two exceptions, the loss of the dicrotism was associated with a decrease in heart rate (to 94 or below) One of the exceptions involved a 40-year-old man who was still in congestive failure with a heart rate of 115 beats per minute but who had lost the dicrotic pulse with a rate of 100 beats per minute that had been present when he was examined at age 36. The pulse of 4 of these patients became dicrotic with the occlusive maneuver however Each one of these 4 had continuing evidence of congestive failure.

Pressure tracings as recorded through catheters the ascending aorta were dicrotic 3 out of 11 patient with cardiomyopathy below the age of 40 In 2 of the 3 the t of rise and fall of the left ventricular pressure tracing was grossly decreased the smooth pointed contour of the

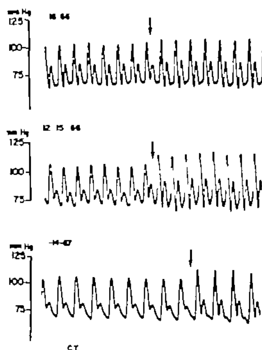


Fig. 7 Progressive disappearance of dicrotism i the brachial artery during convalescence of 39-year-old Caucasian man with cardiomyopathy Heart rate has fallen from 115 (*11 16-64*) to 94 beats per minute (*2 14-67*). Arrow indicates application of occlusive pressure to the artery just distal t the indwelling needle.

tracing having the shape of an isosceles triangle (Fig 8) Pressure tracings from the brachial artery were borderline dicrotic in these 2 and fully dicrotic in the third. It is of interest that an indirect carotid artery pressure tracing obtained in 1 did not reflect the dicrotism simultaneously recorded in the aorta. Of the remaining 8 not having dicrotism in the ascending aorta, 6 nevertheless were fully dicrotic and 2 borderline dicrotic in the brachial artery during the same catheterization.

Other observations made during this study merit brief mention

1 Several patients with cardiomyopathy showed marked spontaneous variations in the degree of dicrotism during the course of one hemodynamic study

2 Marked dicrotism recorded through a catheter in one brachial artery was not present in a simultaneous recording taken from a No 20 Riley needle in the other brachial artery Partial or complete occlusion in this instance by the catheter simu

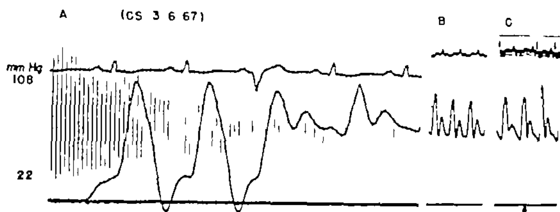


Fig 8 1 Catheter pull-back from the left ventricle to the aorta. Note the slow rate of rise and fall of the left ventricular pressure with dicrotism in the ascending aorta. Time lines 0 04 second. *B* Aortic tracing at slower paper speed *C* Brachial artery pulse also at slower paper speed arrow indicates application of occlusive pressure to the distal artery

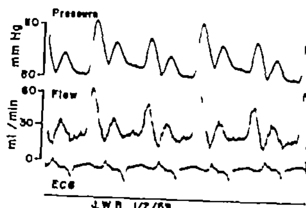


Fig 9 Electromagnetic flowmeter recording from right brachial artery and simultaneous intravascular pressure recording from left brachial artery Time lines 0.1 second.

larly influenced the contour of tracings obtained by external recording devices *simultaneously exerting pressure on the* artery

3 The brachial artery pressure curve of a subject with cardiomyopathy rarely has more than one peak during systole

4 Electromagnetic flowmeter studies (Fig 9) show that the pattern of dicrotism is a matter of flow as well as pressure

Discussion

Scientific knowledge of the dicrotic pulse had its beginnings for the most part with the introduction of Marey s[4] sphygmograph in 1863 M'Vail[5] tells us that physicians and the medical literature for a generation before that date had neglected the palpably double pulse as their attention was increasingly diverted to the newly acquired stethoscope of Laennec. Conditions laid down by Marey for increasing the dicrotic wave were summarized by Fleming[6] (1881) as a fast pulse elastic vessels, feeble tension in the vessels and a small quantity of fluid injected with each ventricular systole. These conditions were generally accepted by the turn of the century In 1906 Lewis[3] stated that systolic pressures of 80 to 125 mm Hg are in the usual range where the pulse may be dicrotic but he also called attention to an important exception where dicrotism was associated with a systolic pressure of 180 mm Hg

Scattered reports in the literature also disclose the previously recorded association of dicrotism with cardiomyopathy although Braunwald and Aygen [7] Ewy Rios and Marcus [8] and Meadows, Osadjan and Sharp[9] are the only ones to have commented on it In 1902 MacKenzie[10] included descriptions of 3 cases of degeneration of the heart muscle due to alcohol in his monograph and stated that the pulse of one was quick soft and dicrotic—one hundred per minute Sanderson[11] appears to have referred to a similar nonalcoholic case in 1867 More recently the dicrotic brachial artery pressure tracings of 4 cases of cardiomyopathy have been included in articles by Balchum McCord and Blount [12] Braunwald and Aygen [7] Yu and co-workers [13] and Marx and Yu [4] while a text by Fowler[15] shows an indirect carotid tracing

with a dicrotic contour taken on a 20-year old patient with postpartum cardiomyopathy. It is also of interest that Wood[16] observed a conspicuous dicrotic wave in 75 per cent of cardiomyopathy cases and commented on its value in the differential diagnosis of the latter from aortic stenosis in severe failure. Finally it must be noted that 3 of 12 indirect carotid tracings taken by Benchimol, Dimond, and Shen[17] on patients with heart failure due to ischemic heart disease were dicrotic.

Ewy and associates[7] recently reported hemodynamic studies of nine patients with a dicrotic brachial artery pulse are in close agreement with our observations. In both groups approximately 80 per cent were instances of congestive cardiomyopathy, and about three fourths were below the age of 40, the remainder being under 50. All had evidence of myocardial failure or compression, and 90 per cent of both series had heart rates which exceeded 92 beats per minute. The mean resting stroke volume was 17 ml. per square meter body surface area (BSA) (range 12 to 26) in Ewy's series and was 25 ml. per square meter BSA (range 11 to 33) in ours; normal > 35 ml. per square meter BSA. The finding of a low stroke volume incidentally is in accord with observations that dicrotism is more likely to appear or become accentuated with the beats following the shorter diastoles of various arrhythmias, the weaker beats of pulsus alternans, the straining phase of a normal Valsalva maneuver, and the inspiratory phase of respiration.[9,11,13] The age incidence suggests a relationship to the progressive loss of arterial elasticity that occurs after the early forties. Ewy, Rios, and Marcus, unfortunately, do not give their criteria for dicrotism other than to state that each had a palpable dicrotic carotid pulse and that the average heights of the notch and wave of the brachial artery tracing were 10 and 44 per cent of the pulse pressure, respectively. It is reasonable to assume then that one or more of their cases must have had a notch above 10 per cent of the pulse pressure and were therefore not fully dicrotic by our criteria.

Ewy's group concluded that the dicrotic arterial pulse is apparently determined by the presence of certain hemodynamic factors in relatively young patients, but that it is not necessarily related to a specific disease entity such as congestive cardiomyopathy. It is apparent from both studies that relative youth, tachycardia, and myocardial failure are important determinants of the dicrotic pulse. We also believe that the frequency of its occurrence in cardiomyopathy in both studies warrants the conclusion that dicrotism is as characteristic of cardiomyopathy under these conditions as it is said to be of typhoid and that it has importance to the pathophysiology and the constellation of physical findings of this disease. Admittedly it is not found exclusively in cardiomyopathy. Actually the frequency of its occurrence in other cardiac entities under the above conditions is yet to be determined.

Both studies contained a minority of patients other than those with cardiomyopathy who had dicrotism (pericardial tamponade, arteriosclerotic heart disease, and hypertensive heart disease[8]) and Ewy refers to the occurrence of dicrotism in primary pulmonary hypertension and constrictive pericarditis. Our material suggests, however, that it occurs infrequently in common types of heart disease other than cardiomyopathy and possibly pericardial tamponade. This is supported by the many published studies of the carotid and brachial artery pulses of valvular and other types of heart disease which, although resulting in descriptions of characteristic pulses for lesions of the aortic valve and left ventricular outflow tract, have nevertheless made no mention of dicrotism.

Apart from other factors that may also be playing a role, it seems probable that arterial aging contributes to the infrequent occurrence of dicrotism in hypertensive and arteriosclerotic heart disease as well as in pure aortic stenosis. Congestive failure generally does not develop in these diseases before the age of 40. Despite these considerations, we believe that further studies of the pulses of various types of heart disease combining youth, a sinus tachycardia, congestive failure, and possibly normotension (excepting hypertensive heart disease) are in order. When one considers, however, the infrequency with which valvular heart disease (especially mitral lesions), primary pulmonary hypertension, cor pulmonale

secondary to chronic lung disease and constrictive pericarditis are seen under these conditions, it does not appear that such a study with adequate numbers will be easily or quickly accomplished.

Nevertheless, a recent report indicates that work along these lines has already begun. Barner, Willman, and Kaiser[24] found that dicrotism appeared and lasted for as long as 1 to 2 months in 34 per cent of patients undergoing prosthetic replacement of a regurgitant aortic valve; this was in contrast to an incidence of 3.5 per cent after all open heart operations and 0.5 per cent after the correction of aortic stenosis. The disappearance of the dicrotism with the development of a leak around the prosthesis and its return on repeated occasion with repair of the dehiscence suggests the importance of a competent aortic valve in the development of dicrotism. One is also drawn to a consideration of possible similarities in the pathophysiology of this situation and cardiomyopathy.

Approximately one third of the dicrotic pulses as measured directly were poorly detected by palpation. The reasons for this unexpected finding are obscure; it cannot be explained by differences in systolic or pulse pressure or the degree of dicrotism. On the other hand, pulses were palpably double when the direct recording was not dicrotic by our criteria. This situation was due, in some instances, to a high dicrotic notch (>20 per cent pulse pressure) followed by a prominent dicrotic wave. The pulses of 2 patients with hypertensive heart disease fell into this category. A variation of this type of pulse is one which has prominent percussion and tidal waves in addition. This "trifid" pulse was found with distal compression in 21 patients with various types of heart disease and it was frequently palpable. Since all of these pulses as well as the classic bisferiens pulse give the impression of a double impulse to the examining fingers, the interpretation of the particular pulse in the absence of a direct or indirect recording rests largely on inference depending on the type of heart disease which is present. It should also be recognized that the pulse as palpated is the result of partial or complete occlusion of the artery. One therefore cannot predict with certainty the form of the unoccluded pulse when palpating a double arterial impulse.[11]

The mechanism of production of the dicrotic pulse is beyond the scope of this study. Nevertheless, we have been intrigued by the transition from a bisferiens-like contour to dicrotism that occurs with the low pressure beats of arrhythmias, the straining phase of a normal response to the Valsalva maneuver, and the inspiratory phase of respiration. It is particularly well illustrated during the Valsalva maneuver where with straining the tidal (predicrotic) wave becomes progressively lower on the catacrotic limb to finally merge with an increasing dicrotic wave and deepening dicrotic notch. These changes occur concomitantly with a decreasing stroke volume and velocity of ejection and thus resemble the situation in cardiomyopathy. The bisferiens pulse, on the other hand, is frequently associated with clinical conditions giving rise to a high stroke volume and velocity of ejection. It would appear, then, that the tidal and dicrotic waves have a reciprocal relationship as regards stroke flow. Wiggers[3] adds vessel elasticity as a further determinant of this relationship.

"The more nearly vessels approach conditions which obtain in rigid tubes, the more rapidly the reflected waves are propagated. Consequently, when pressures are reasonably high and the peripheral outflow during the last portion of systole does not greatly exceed the cardiac input per unit time, predicrotic waves are common. When the elastic resistance in the arteries is reduced below normal, either by vasodilation or by changes in cardiac ejection which diminish the output greatly during the latter portion of systole, reflected waves travel more slowly. Under such conditions they may arrive in the radial artery synchronously with the dicrotic elevation. When this occurs, the two waves summate and a larger dicrotic wave is produced. . . . any change in the primary wave which causes the disappearance of the predicrotic wave gives the pulse a more dicrotic appearance."*

The accentuation or production of dicrotism by arterial compression at or distal

*Quoted with permission from Wiggers, C. J.: The Pressure Pulses in the Cardiovascular System, New York, 1928, Longmans, Green and Company, p. 82.

to the recording point is an old observation about which nothing further appears to have been written.[1,10-14] As a working hypothesis we consider it to be an unmasking of otherwise latent dicrotism where conditions are suboptimal for its full expression, e.g., aging arteries or improvement in the congestive failure. It is of interest, however, that dicrotism with distal pressure also occurred in one of the control subjects, a 42 year-old Negro man in mild diabetic acidosis who was also having withdrawal symptoms from heroin addiction. Heart rate was 94 beats per minute, and blood pressure was 108/62 mm. Hg. Two weeks later dicrotism with distal pressure was present only during inspiration. A right heart catheterization at this time revealed normal pressures and flows.

Summary

Dicrotism of the brachial pulse as seen in this laboratory is highly correlated with congestive cardiomyopathy and pericardial tamponade when these diagnoses are made on patients below the age of 40 who have a heart rate over 90 beats per minute (in regular rhythm). When not present otherwise, the phenomenon may be elicited by occlusive pressure at or just distal to the point from which it is being sensed, and under these circumstances age drops out as a major determinant of its occurrence. Observations from the previous literature as well as from this laboratory also indicate that dicrotism probably occurs with much less frequency in the presence of elevated blood pressures. Barner, Willman, and Kaiser's[8] experience during the early period following prosthetic replacement of the regurgitant aortic valve and our own with cardiomyopathy suggest that certain cardiac disease states may be more likely than others to give rise to dicrotism. There is a need for further clarification of this possibility. Such a study should include significant numbers of all types of heart disease, but it should also be done, insofar as is possible, in the presence of all those other factors known to favor dicrotism.

Historically, the dicrotic pulse appears to have excited the attention of clinicians of the last third of the nineteenth century as a part of the new knowledge obtained from the sphygmograph introduced by Marey in 1863. As the sphygmograph fell into disuse with the appearance of the sphygmomanometer and the string galvanometer, interest in the dicrotic pulse also waned, and it is only now, late in the resurgence of interest in pulses afforded by the introduction of modern electronic transducers, that dicrotism is again presenting itself for study. It should be recognized that many of the factors giving rise to dicrotism were known to writers of this earlier period.

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Exercise test, history, and serum lipid levels in patients with chest pain and normal electrocardiogram at rest: Comparison to findings at coronary arteriography

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In several clinical and pathologic studies[1-4] the electrocardiogram (ECG) taken at rest was found to predict atherosclerotic heart disease in a disappointingly low proportion of cases. The same was discovered in practically all studies relating the ECG to findings at coronary arteriography.[4] In our own material the ECG taken during rest was found to be normal in as many as 51 per cent of the patients with angiographically proved obstructive coronary artery disease.[5,*]

In order to derive more diagnostic information from the electrical activity of the heart, exercise tests are widely employed. For this purpose Master's[14] two-step test has been used universally for many years. However, judging from the literature, there is a growing inclination to use graded exercise tests (GXT) with maximal or submaximal work load instead. While the GXT would seem more promising from a theoretical standpoint, there is still a relative lack of published data to substantiate this supposition. We have examined the results of a GXT and a modified Master's two-step test in data from 96 patients with chest pain and a normal ECG taken at rest. The results were compared to findings at coronary arteriography.

The purpose of this study was to gain better information relative to (1) the diagnostic value of the two exercise tests, (2) the discriminative value of commonly applied criteria, (3) the diagnostic information which can be derived from various diagnostic parameters (exercise tests, history, and serum lipid levels) singly and jointly.

Material, methods, and criteria

Patient material. From the total data of more than 1,000 selective coronary arterio-

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*Vectorcardiograms were also taken in all cases. However, since selection was made of patients with normal ECG, the results of the vectorcardiographic studies were not included.

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CAG was considered to represent the reality Only binary statements (yes-or-no) were admitted

In order to display conveniently the relation between prediction and reality in the entire series, use was made of contingency tables (Table I) In the table a_1 through a represent the number of correct-positive, false-negative false positive and correct-negative predictions, respectively For each parameter the fraction correct-positive predictions of the total number of positive cases $(\frac{a}{a_1 + a_1})$ and the fraction correct negative predictions of the total number of negative cases $(\frac{a}{a_3 + a_4})$ was calculated

The fact that two figures are required to characterize the relation between prediction and reality makes the comparison of the diagnostic performance of different parameters less perspicuous. Therefore, in addition a single association index was calculated for which purpose the index of merit (T) devised by Kuipers[17] was applied

$$T = \frac{a}{a_1 + a} + \frac{a}{a + a} - 1$$

It follows that T ranges from 0 (no association) to 1 (perfect association)

Standard deviations were also calculated

$$s(T) = \frac{[4p(1-p)]^{-} - T^2}{\sum_i a_i} \text{ in which}$$

$$p = \frac{a_1 + a}{\sum_i a}$$

Results

Coronary arteriographic findings Application of our grading scale in the 96 patients yielded the following distribution Grade 0 41 patients Grade 1 11 patients Grade 2 22 patients Grade 3 22 patients. Thus there were 52 subjects in whom the coronary arteries were either normal or showed only slight narrowings (Grades 0 and 1) These subjects were considered to have a negative CAG

In the other 44 patients (Grades 2 and 3)

Table I Contingency table a_1 through a_4 represent the numbers of correct positive false-negative false-positive and correct negative predictions respectively

		Prediction	
		+	−
Reality	+		a
	−	a_4	a_4

the CAG was classified as positive. A total of 24 occlusions was noted in the 22 patients of Grade 3 the localization being as follows right coronary artery 14 anterior descending artery 7 and circumflex branch 3

Graded exercise test (GXT)

RESPONSES AND RELATION TO THE CAG The positive (ischemic) and negative (non ischemic) responses and the distribution over the 4 grades of the CAG are presented in Fig 1

In 29 subjects an ischemic response (sagging 10 horizontal 19) was noted In 26 of these patients the CAG was positive (more than 50 per cent narrowing Grades 2 and 3) in the other 3 patients the CAG was negative (Grades 0 and 1)

The remaining 67 patients had a negative GXT This was associated with a positive CAG in 18 subjects and a negative CAG in 49 patients. Among the 18 false negative responders there were 6 patients (out of 7 in the total material) with isolated obstruction of the right coronary artery in the remaining 12 patients the arteriographic abnormalities were basically the same as in the 26 correct-positive subjects.

The responses observed in the subjects with a negative GXT were the following no change or junctional depression < 2 mm 55 patients junctional depression ≥ 2 mm 9 patients repetitive ventricular extrasystoles, 3 patients. Of the 9 patients with a junctional depression of 2 mm. or more, only 3 had a positive CAG in 1 of the 3 with repetitive ventricular extrasystoles, the CAG was also positive. Thus, in both categories the number of the posi

grams (CAG's) performed in our department a series of 96 patients all recently studied because of chest pain was selected. Requirements for inclusion in this series were: (a) the ECG taken at rest had to be essentially normal (cases with slight atypical repolarization disturbances or slight intraventricular conduction disturbances however were not excluded); (b) no other cardiac abnormalities than those related to ischemia should be present. There were 11 women and 85 men; ages ranged from 30 to 63 years (mean age, 46.2 ± 6.2 years).

Coronary arteriography (CAG). All patients underwent selective coronary arteriography following Sones technique[14] with the use of multiple left and right anterior oblique projections. The 5 inch field of an interchangeable 5 and 9 inch Philips image intensifier linked with a cine pulse unit was employed. Recordings were made on 35 mm. film with a speed of 60 frames per second.

Classification of the severity of arterial disease was made according to the severest narrowing in any of the major branches (right coronary artery, main left coronary artery, anterior descending and circumflex branches). The following arbitrary grading system was used: Grade 0, normal; Grade 1, vascular wall irregularities causing narrowings of less than 50 per cent of the lumen diameter; Grade 2, more than 50 per cent narrowing but no occlusion; Grade 3, total occlusion.

Graded exercise test (GXT). Digitalis preparations were withheld for 3 weeks prior to the test. No antianginal drugs (including beta blocking agents) were administered on the day of testing; a light breakfast was allowed.

A calibrated bicycle ergometer was used. Exercise was begun with a work load of 15 watts and was augmented in steps of 15 watts every 90 seconds until any of the following appeared: (1) angina pectoris, (2) inability of the patient to continue, (3) ischemic S-T depressions ≥ 0.2 mv., (4) heart rate exceeding 170 beats per minute, (5) repetitive ventricular extrasystoles, and (6) atrioventricular conduction disturbances.

Extremity electrodes were placed as described by Mason and Likar[11]; 6 precordial electrodes were placed in standard positions; careful attention was paid to electrode attachment and skin preparation.

Recordings were made throughout the entire procedure with an 8 channel ink jet recorder (Elema Mingograf 81) with paper speeds of 25 and 100 mm. per second and an amplitude calibration of 1 mv. per centimeter. A special switching network allowed rapid successive registration of two groups of 6 leads.

The test was considered to be positive if an ischemic S-T segment depression[12,13] ≥ 0.1 mv. was observed in any lead. The diagnostic value of other responses was also studied.

The double two-step test. A double two-step test according to the method of Master[14] was performed in 91 patients of this series. The set of exploring leads recommended by Master was replaced by a single lead as described by Yu and Soffer.[15]

History. The patient's history was taken in the usual way; in addition questionnaires were used which were filled out by the patient himself. Typical angina pectoris was considered to be present if the localization of the pain included some area of the left hemithorax and if the following criteria were fulfilled: (1) the pain had to be provoked by physical effort, (2) the pain might in addition be precipitated by emotions, cold and sexual intercourse, and (3) the pain should not occur without explicit inducement. The criteria appeared to have optimal discriminative value in previous association studies[6,10] in which the agreement with the CAG could not be improved by taking into account other features such as radiation, quality, and duration of the pain. Chest pains which did not meet these criteria were listed as atypical.

Laboratory methods. The serum cholesterol was determined according to the method of Rappaport (sulfosalicylic acid and acetic anhydride) and the serum beta lipoprotein was determined with the beta L test (Hyland); the length of the precipitate column was taken as a measure for the beta lipoprotein content. Fasting specimens were used.

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Table III Total number of ischemic S-T segment changes in separate leads observed in 29 subjects at GXT

Lead	*I*	*II*	*III*	*V*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	*Total*
Number*	0	6	5	0	6	1	15	25	26	84
Percentage†	0	17 5	14 5	0	17 5	3	52	86	90	

*Number of ischemic S-T segment changes in separate leads.
†Percentage of the 29 patients detected if only this lead were recorded.

Table IV Patients with pathologic S-T changes in Leads II III or aVF Relation to the grade and localisation of the coronary obstructions

Patient	*Grading of separate branches**				
	Left coronary artery				*Right coronary artery*
	Main	*Anterior descending*	*Circumflex*		
			Main	*Obtuse margin*	
1	1	3	0	2	3
2	0	3	0	0	0
3	0	2	1	0	3
4	2	2	2	0	1
5	0	0	0	0	0
6	1	0	0	2	2

*0, normal 1, 0 to 50 per cent narrowing of lumen diameter; 2, more than 50 per cent obstruction but not total; 3, occlusion.

Table V Maximal heart rate and maximal work load by GXT in the 44 patients with a positive CAG

	No. of patients	*Maximal heart rate (beats/min.)*	*Maximal work load (watts)*
Positive GXT	26	127(±20)	88(±21)
Negative GXT	18	143(±30)	115(±25)

represents the contingency between the two-step test and CAG It follows that the correct positive fraction = 0.33 the correct negative fraction = 0 93 and T = 0.26 (± 0 10)

GXT versus two-step test From the indices of merit it appears that the GXT discriminated better between a pathologic and a normal coronary system than did the two-step test. The difference resulted from a higher correct positive fraction by the GXT In 13 subjects with positive CAG the prediction by the GXT was correct whereas the two-step test yielded a false negative result.

Table VII shows that the maximum work load in these 13 subjects had not been higher than in the other correct-positive responders (who had a positive two-step test) the mean total work performed was 1 989 kg m.

Conversely subjects in whom coronary

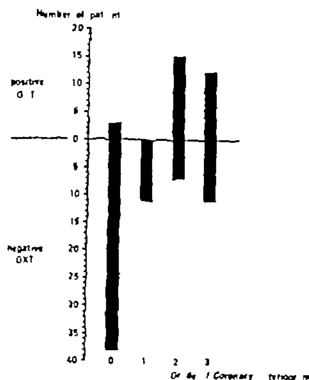


Fig. 1. Results of the graded exercise test (GXT). Distribution of positive and negative cases over the 4 grades of coronary arteriogram.

tive CAG's was below the a priori probability and these criteria had to be considered as nondiscriminative.

THE INDEX OF MERIT. From the results described in the preceding paragraph the contingency table (Table II) can easily be derived. It follows that the correct positive fraction = $\frac{26}{44}$ = 0.59 and the correct negative fraction = $\frac{49}{52}$ = 0.94. The index of merit = 0.53 (± 0.08).

LOCALIZATION OF ISCHEMIC S-T CHANGES. In the 29 positive responders a total of 84 ischemic S-T segment changes was detected (Table III). There were 6 patients in whom ischemic changes occurred in the extremity leads (I, II, III, aV_L, or aV_F). However, in all these patients ischemic responses were also noted in the precordial leads which actually appeared even earlier than those in the extremity leads. With regard to the precordial leads it appeared that ischemic changes in Leads V_3 and V_4 were invariably associated with ischemic changes in Leads V_5 or V_6. In other words, recording of Leads V_5 and V_6 only would have sufficed to detect all positive cases! It might be expected that in patients showing ischemic

*Table II. Relation between coronary arteriogram and graded exercise test**

		GXT		
		+	−	Total
CAG	+	26	18	44
	−	3	49	52
Total		29	67	96

*Correct positive fraction: $\frac{26}{44}$ = 0.59. Correct-negative fraction: $\frac{49}{52}$ = 0.94. Index of merit: $\frac{26}{44} + \frac{49}{52} - 1$ = 0.53 (± 0.08).

changes in Leads II, III, or aV_F, the vascular supply to the diaphragmatic wall of the myocardium (provided by the terminal branches of the right and the circumflex arteries) was impaired. In 4 of the 6 patients at least one of these branches was involved (Table IV). However, severe lesions of the anterior descending artery were also present in 4 subjects, and since isolated obstructions of the right coronary artery yielded in all but one case a negative GXT, it seems that positive responses in the extremity leads were rather an expression of diffuse coronary disease.

WORK LOAD AND WORK PERFORMANCE. The mean maximum heart rate and maximum work load in the 44 patients with a positive CAG are shown in Table V. The maximum work load and the maximum heart rate were not higher in the correct positive responders than in the false-negative responders. In the 3 patients with a false-positive response the maximum work load had not been excessively high (ranging from 90 to 120 watts). It can be calculated that in the correct positive cases the mean total work performed at GXT was 2,189 kg m.

Two-step test. In 91 subjects a two-step test was performed. Ischemic S-T changes occurred in 17 subjects; in 13 of these the CAG was positive and in 4 the CAG was negative. In the remaining 64 subjects no changes or junctional depressions of less than 2 mm. were observed. Of the latter category, 26 patients had a positive CAG and 48 had a negative CAG. Table VI

mutual independency i.e. history GXT and serum β-lipoprotein were studied in combination. First the subjects in whom these 3 parameters were concordant (all being either positive or negative) were singled out. In 30 patients (31 per cent of the total patients) such a combination was encountered the prediction was positive in 15 of these and negative in the other 15 In this group the association with the CAG was excellent there was only one patient in whom the prediction was false positive, and there were no patients with a false negative diagnosis (Fig 2) The index of merit was as high as 0 93

In 34 subjects the statement by history and GXT were concordant, but the serum β-lipoprotein level was at variance. If these subjects are added to the previous 30 patients, the number of patients in whom the statements by GXT and history were in agreement amounts to 64 (Fig 2) For this category the correct-positive fraction and the correct negative fraction were 0 85 and 0 97 respectively and T = 0.82 In the remaining 32 subjects, in whom the statements by GXT and history were contradictory the highest index of merit was obtained if the decision was based on the serum β-lipoprotein level In other words, for the entire group of 96 patients an optimal association with the CAG was gained if the diagnosis was made according to 2 or 3 concordant parameters. The result of this procedure is represented by Table IX It follows that the correct

Table IX Contingency table for the entire group of patients if the decision is made on the basis of 3 independent parameters (history GXT and serum β-lipoprotein)

		2 or 3 methods		Total
		+	−	
CAG	+	36	8	44
	−	7	45	52
Total		43	53	96

% correct positive fraction .82. Correct-negative fraction .85. Index of merit .67

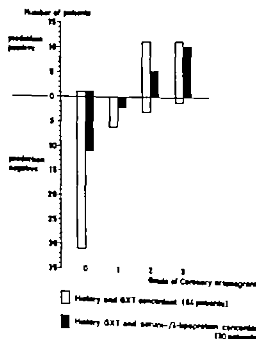


Fig 2 Patients in whom the statements by either GXT and history or GXT history and serum β-lipoprotein level were concordant. Distribution of positive and negative cases over the 4 grades of coronary arteriogram.

Table X Results of GXT and comparison to coronary arteriographic findings by different author

Author	No. of patients	Correct-positive fraction	Correct-negative fraction	Index of merit
Kasselbaum, Sutherland and Judkins[11]	68	0 51	0 96	0 47(±0 11)
Mason et al.[19]	84	0 77	0 89	0 66(±0 08)
Roitman, Jones and Sheffield[20]	46	0 80	0 87	0 67(±0 12)
This report	96	0 59	0 94	0 53(±0 08)

obstructions were correctly predicted by the two-step test but not by the GXT were not encountered

The history. According to our criteria, 50 patients had a history of typical angina pectoris and 46 patients had atypical chest pain. The relation to the CAG was as follows: correct positive fraction = 0.84; correct negative fraction = 0.75; T = 0.59 (± 0.08).

The serum lipids. As for the history, the bisection between normal and abnormal was made in retrospect. It appeared that the optimal cutting points were somewhat higher than the upper limits of normality by the laboratory standards, namely, serum cholesterol 280 mg. per 100 ml. and serum β-lipoprotein 3 mm.; this was in agreement with previous observations.[4,19]

SERUM CHOLESTEROL. Correct positive fraction = 0.52; correct negative fraction = 0.76; T = 0.28 (± 0.10).

SERUM β-LIPOPROTEIN. Correct-positive fraction = 0.89; correct negative fraction = 0.48; T = 0.37 (± 0.09).

Joint predictive value. The association for the diagnostic methods which were included in this study with the CAG are summarized in Table VIII. When arranged according to the magnitude of the index of merit, the order is history, GXT, serum β-lipoprotein, serum cholesterol, and two-step test. It was expected that a combination of diagnostic parameters would yield a better result than the parameters singly. Therefore, the three methods which showed the highest indices of merit together with a high degree of

*Table VI. Relation between CAG and two-step test**

		Two-step test		Total
		+	−	
CAG	+	13	26	39
	−	4	48	52
Total		17	74	91

*Correct positive fraction = 0.33. Correct negative fraction = 0.93. Index of merit = 0.26 (± 0.10).

Table VII. Twenty-six patients with positive coronary arteriographic findings and positive GXT divided according to whether the two-step test was positive or negative. Relation to maximal work load and maximal heart rate

	No. of patients	GXT test		Two-step test
		Maximal heart rate (beats/min.)	Maximal work load (watts)	Maximal heart rate (beats/min.)
Positive GXT and positive two-step test	13	129 (±21)	96 (±20)	126(±13)
Positive GXT and negative two-step test	13	125 (±18)	83 (±21)	121(±23)

Table VIII. Discriminative skill of diagnostic methods which were included in this study

Method	Correct positive fraction	Correct negative fraction	Index of merit
History	0.84	0.75	0.59(±0.08)
GXT	0.59	0.94	0.53(±0.08)
Serum β-lipoprotein	0.89	0.48	0.37(±0.09)
Serum cholesterol	0.52	0.76	0.28(±0.10)
Two-step test	0.33	0.93	0.26(±0.10)

mutual independency i.e. history GXT and serum β-lipoprotein were studied in combination First the subjects in whom these 3 parameters were concordant (all being either positive or negative) were singled out. In 30 patients (31 per cent of the total patients) such a combination was encountered the prediction was positive in 15 of these and negative in the other 15 In this group the association with the CAG was excellent there was only one patient in whom the prediction was false-positive and there were no patients with a false negative diagnosis (Fig 2) The index of merit was as high as 0 93

In 34 subjects the statement by history and GXT were concordant, but the serum β-lipoprotein level was at variance. If these subjects are added to the previous 30 patients, the number of patients in whom the statements by GXT and history were in agreement amounts to 64 (Fig 2) For this category the correct-positive fraction and the correct negative fraction were 0.85 and 0 97 respectively and T = 0.82 In the remaining 32 subjects in whom the statements by GXT and history were contradictory the highest index of merit was obtained if the decision was based on the serum β-lipoprotein level In other words for the entire group of 96 patients an optimal association with the CAG was gained if the diagnosis was made according to 2 or 3 concordant parameters. The result of this procedure is represented by Table IX. It follows that the correct

Table IX. Contingency table for the entire group of patients if the decision s made on the basis of 3 independent parameters (history GXT and serum β-lipoprotein)

		2 or 3 methods		Total
		+	–	
CAG	+	36	8	44
		7	45	52
Total		43	53	96

*Correct-positive fraction 0 82. Correct-negative fraction 83. Index of merit

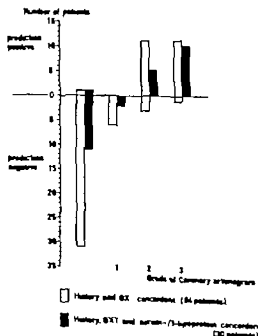


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This report	96	0 59	0 94	0 53(±0 08)

positive fraction = 0.82, the correct negative fraction = 0.85, and T = 0.67.

Discussion

In order to be able to compare our findings to the results obtained by other investigators, we have applied the same statistical calculations to studies dealing with the relation between coronary arteriography and the GXT (Table X). It appears that our results are in good agreement with the findings reported in the literature.

In our material the diagnostic performance of the GXT was significantly better than that of the two-step test ($p < 0.01$). The difference resulted from a higher fraction correct positive prediction.

A review of the literature revealed no comparative exercise test studies with the use of the coronary arteriogram as a reference. However, more correct positive responses by the GXT were also reported by Mason and co-workers,[19] Sheffield, Holt, and Reeves,[21] and Bellet and Roman[22] in patients with a clinical diagnosis of angina pectoris.

One might suppose that in our material the GXT compared favorably to the two-step test because more leads were employed. However, it seems unlikely that this could be the only explanation. First, in 86 per cent of the positive cases by the GXT an ischemic response was found in Lead V_4; if only this lead were recorded the GXT would still score definitely higher than the two-step test. Second, in the above-mentioned studies,[19,21,22] the GXT yielded more positive diagnoses than the two-step test, although multiple leads were used in both. Therefore the difference has to be explained mainly by either the maximum work load or the total work performed. In the subjects with a correct positive GXT but a false negative two-step test, the mean maximum work load and total work performed were 83 watts and 1,989 kg m., respectively. It has been calculated that the (maximum) work load in the two-step test is approximately 75 watts.[22] Consequently, the total work performed in three minutes is 1,440 kg m. Thus the total work performed appears to be the most influential factor. Although the diagnostic gain from GXT appeared to be considerable in our series of patients who all had a normal ECG at rest, it should be noted that the test failed to show ischemic changes in 41 per cent of the patients who had marked coronary artery disease disclosed by the CAG. Comparison of these false negative subjects to the correct-positive responders revealed that the first group comprised a relatively high proportion of patients with isolated obstruction of the right coronary artery, while the maximum work load, the total work performed, and the maximum heart rate were almost the same in both categories. It would seem, therefore, that inferior wall ischemia is especially difficult to detect. Application of less rigid criteria for a positive GXT (junctional depressions and repetitive ventricular extrasystoles) did result in a small increase of the number of correct positive diagnoses but at the same time entailed a substantial number of false positive predictions, and consequently lowered the index of merit. It is of interest that a positive GXT corroborated by a positive history, or conversely, a negative GXT in conjunction with a negative history, yielded a diagnostic accuracy which was definitely superior to the discriminative skill of the parameters singly. If the serum β-lipoprotein content was also in agreement, the prediction was almost perfect. In 34 per cent of the patients the GXT and the history were discordant; in this group the diagnostic accuracy could be enhanced by leaving the decision to the serum β-lipoprotein content; nevertheless, in the total data the association with the CAG remained far from optimal. It may be hoped that inclusion of more diagnostic parameters will eventually permit further differentiation in such cases. The material presently available is still too limited and too much influenced by selection to warrant definite statistical conclusions, but we feel that there is an indication that continuing multidimensional studies are of great importance in selecting patients for coronary arteriography and that these investigations may constitute a rational basis for epidemiologic studies.

Summary

In a series of 96 patients with chest pain and a normal ECG at rest, the results of a GXT, the history, and the serum lipid

levels were compared to the findings at coronary arteriography In addition in 91 subjects a modified two-step test was performed

To characterize quantitatively and in one number the relation to the coronary arteriogram use was made of the index of merit (T) which ranges from 0 to 1 The following indices were found history 0.59 GXT 0.53 serum β-lipoprotein 0.37 serum cholesterol 0 28 and two-step test, 0 26

In 30 subjects the statements of the history the GXT and serum β-lipoprotein were concordant. In this category the agreement with the coronary arteriogram was excellent (T = 0 93)

In 64 subjects the statements by the history and the GXT were concordant, but the serum β-lipoprotein level was at variance. For this group T = 0.82 For the entire series the best result was obtained if the decision was made according to two or three identical statements, which resulted in an index of merit of 0 67

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Wedge arteriography for the identification of pulmonary emboli in small vessels

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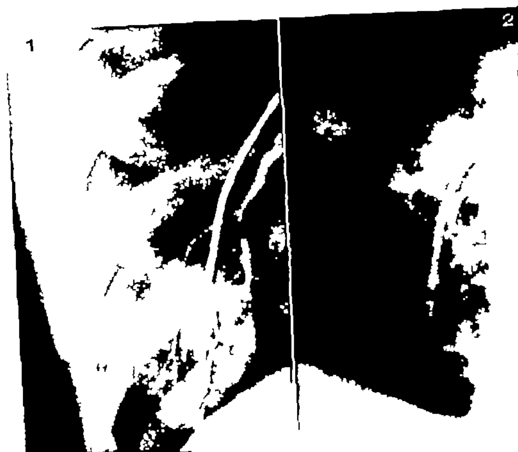
Pulmonary arteriography has been shown to be highly specific for the diagnosis of acute pulmonary embolism.[1-3] Even though a correct diagnosis can be established by pulmonary arteriography in a large majority of instances, there are patients in whom pulmonary arteriograms are not diagnostic. The most specific arteriographic signs—filling defects and cut off vessels—are particularly subject to errors of interpretation in peripheral vessels due to a low concentration of contrast material in these areas. Consequently, emboli located in peripheral arteries may be overlooked. This is the case even when selective injections are made into the right or left pulmonary artery. The presence of emboli in such vessels would be indicated only by inference because of the occurrence of hypoperfusion or delayed arterial filling, which are nonspecific roentgenographic signs. The purpose of this communication is to demonstrate the efficacy of pulmonary wedge arteriography for the recognition of pulmonary emboli lodged in small (1 to 2 mm. diameter) arteries. Emboli in small pulmonary arteries are almost always associated with emboli in large arteries, but they may occur independently.[3] The recognition of emboli in small vessels is important because it may substantiate the diagnosis in otherwise equivocal cases and it may call attention to sites of obstruction not otherwise apparent.

Methods

The ability of pulmonary wedge arteriograms to show pulmonary emboli in small arteries was demonstrated in two patients with proved acute pulmonary embolism. Pulmonary wedge arteriography is performed by positioning the tip of a cardiac catheter in the pulmonary wedge position and injecting 1.0 ml. of contrast material into the distal portion of the pulmonary artery and pulmonary capillary bed.[4] Wedge arteriograms were obtained on single film frames and on 35 mm. cine film[5]; the two methods are supplementary. The former method, using high resolution fine-grain film, showed remarkable detail in the small vessels. The latter method indicated all phases of flow (arterial, capillary, and venous). Consequently, errors of interpretation due to unavoidable variation in the exact volume and pressure of the injection and due to the inability to determine the precise time at which pictures were recorded were eliminated. Pulmonary wedge

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Figs. 1 and 2. Wedge arteriograms. (Fig. 1) Normal pulmonary wedge arteriogram. Vessels narrow gradually and show numerous fine branches. A background blush of capillary filling and veins draining this segment are shown. Vessels of 0.2 mm. diameter can be seen (note comparison with the catheter, which is 2.3 mm. in diameter). (Fig. 2) Wedge arteriogram, patient No. 1, showing completely obstructed artery just distal to the tip of the catheter (arrow). Diameter of occluded artery is approximately 2.0 mm. Contrast material has been forced in retrograde direction due to the obstruction, and is seen along the side of the catheter (arrowhead).

Table I. Two patients with acute pulmonary embolism

Patient	*History*	*Physical examination*	*Chest film*	*Arterial* Po_2 *(mm. Hg)*	*PA pressure (mm. Hg)*	*Pulmonary arteriogram*
1	67-yr.-old man, metastatic carcinoma, sudden severe dyspnea	Neck veins distended, râles, accentuated pulmonic closure, S_3 gallop, ankle edema	Infiltrate, left upper lobe	52	64/28	See Fig. 4
2	75-yr.-old man, carcinoma of prostate, syncope and sudden severe dyspnea followed by right pleuritic pain	Neck veins distended, dullness, decreased breath sounds (right base), accentuated pulmonic closure, S_3 gallop, ankle edema	Pleural effusion, right	41	75/20	See Fig. 6

Abbreviations: PA = pulmonary artery; Po_2 = partial pressure of oxygen in arterial blood.



Fig. 3 Wedge arteriogram, patient No. 1 showing intraluminal filling defect in arteries 1.5 to 2.0 mm in diameter. Arteries are outlined by contrast material. Central radiolucencies are apparent.

arteriograms using the single film technique can clearly delineate pulmonary arteries as small as 0.2 mm in diameter[3] and according to Jacobson[4] even smaller arteries can be shown by this method. One ml of 60 per cent meglumine diatrizoate (Hypaque-meglumine) was injected through the wedged catheter and a single film was taken just at the conclusion of the injection using Cronex II film* mounted in a cardboard cassette with a single Radelin† ultradetail screen. Cine pulmonary wedge arteriograms were then obtained by flushing the residual contents of the catheter while recording on 35 mm Kodak double X film at 64 frames per second. An example of a normal wedge arteriogram is shown in Fig. 1. A maximum of 2 ml of contrast material was used for each set (cine film and single frame) of wedge arteriograms. Studies in the laboratory using this technique showed that the pressures at the tip of the catheter varied from 300 to 500 mm Hg which is of course considerably higher than the pressure of blood flowing through these vessels. However, no abnormal arteriovenous communications were caused by this relatively high injection pressure in 20 normal dogs

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Fig. 4 Pulmonary arteriogram, patient No. 1. Bilateral filling defects and cut off vessels are shown.

and more than 90 patients studied during cardiac catheterization.

Two patients with unquestioned clinical hemodynamic, and arteriographic evidence of acute pulmonary embolism were studied (Table I) Pulmonary arteriograms were obtained according to the techniques previously described.

Results

Pulmonary wedge arteriograms in both patients showed emboli in pulmonary arteries of less than 2.0 mm diameter These arteriograms, together with arteriograms taken in the proximal portion of the pulmonary artery are presented in Figs. 2 to 6. The abnormalities on the wedge arteriograms are readily apparent, especially when these arteriograms are compared to normal pulmonary wedge arteriograms (Fig 1) In arteriograms of normal subjects, one sees gradual tapering of the small pulmonary arteries from the site of injection to the capillary bed The walls of the vessels are smooth and there are numerous fine branches. A background blush of capillary filling is apparent and small veins that drain the pulmonary segment are clearly visible. By contrast, wedge arteriograms in the two patients with acute pulmonary embolism showed completely obstructed (cut off) arteries just distal to the tip of the catheter (Figs. 2 and 5) these obstructed vessels were no larger than the diameter of the catheter (2.3 mm.) Contrast material was forced in a retrograde direction around the walls of the catheter Cine wedge arteriograms taken at the same site confirmed the fact that the arteries were occluded These cine arteriograms eliminated the possibility of partial filling being mistaken for a cutoff vessel such a misinterpretation could occur due to the chance timing of a single film arteriogram Intraluminal filling defects in arteries of 1.5 to 2.0 mm in diameter were shown to be present in one patient (Fig 3) Small arteries were outlined by contrast



Fig. 3. Wedge arteriogram, patient No. 1 showing intraluminal filling defects in arteries 1.5 to 2.0 mm. in diameter. Arteries are outlined by contrast material. Central radiolucencies are apparent.

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Fig. 6. Right pulmonary arteriogram, patient No. 2. Artery to right lower lobe completely occluded. Tortuous, pruned vessels can be seen in lower zone.

nal—have been described. It is essential therefore that the contrast material be promptly flushed through the pulmonary circulation by isotonic saline and that a safe volume of contrast material (2 ml.) never be exceeded.

Summary

The ability of pulmonary wedge arteriograms to show emboli in pulmonary arteries as small as 1.5 mm. in diameter was demonstrated in two patients. Wedge arteriography may serve as a useful supplemental diagnostic procedure. Identification of emboli in small arteries emphasizes the diffuse involvement of the vasculature in patients with pulmonary embolism.

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Fig. 5. Wedge arteriogram, patient No. 2, showing occluded small artery (arrow) just distal to tip of catheter. As with first patient (Fig. 2), contrast material was forced in a retrograde direction along walls of catheter.

material, but central radiolucencies were shown. No artifacts that could simulate such filling defects were shown in more than 90 patients in whom wedge arteriograms were performed during routine diagnostic cardiac catheterization. Pulmonary arteriograms obtained during bolus injections of contrast material into the main pulmonary artery (Fig. 4) or obtained during the injection of contrast medium into the left or right pulmonary artery (Fig. 6) cannot show emboli of the minute size revealed by wedge arteriograms.

Discussion

Demonstration of pulmonary emboli in arteries of 1 to 2 mm. in diameter serves the following purposes:

1. The method is useful as a supplemental diagnostic procedure, particularly in individuals in whom the large vessel arteriograms are equivocal.

2. The demonstration of emboli lodged in small arteries emphasizes the diffuse involvement and multiplicity of arteries affected in most cases of pulmonary embolism.

3. The method may show emboli in regions of the lung that may not be indicated by large vessel arteriography.

4. Wedge arteriograms serve as a visual indicator of the cause of the decreased blood flow that is manifest on large vessel pulmonary arteriograms as hypoperfusion, slowness of arterial filling, and slowness of venous filling.[1]

Obviously, wedge arteriograms show vessels in only a small area of the lung. Wedge arteriograms should therefore be obtained at several sites in order to increase the likelihood of obtaining positive films.

Hazards of wedge arteriography—particularly localized pulmonary necrosis due to high concentrations of co te

Thirty-one patients had internal mammary implants (20 single implants, 11 double implants), 17 patients had saphenous vein bypass operations, and two patients had endarterectomies or venous patch graft operations. No patient had clinical evidence of left ventricular failure prior to operation. All patients had the diagnosis of severe obstructive coronary artery disease established preoperatively by coronary arteriography.

Treadmill exercise tests were positive in 24 of 30 patients in whom this test was employed. The criterion of a positive test was 1 mm. or more of S-T depression with a duration of 0.08 second or more. Right heart catheterization studies were performed in 24 patients and the resting pulmonary artery (PA) wedge pressure did not exceed 16 mm. in any of these patients. No patients who had persisting symptoms and signs of left ventricular failure were operated upon.

In 19 patients, the preoperative ECG demonstrated a healed infarct pattern. No patients were operated upon who had an occurrence of infarction or a duration of angina or ischemic pain of less than 6 months prior to study.

A 12 lead ECG was recorded prior to surgery and daily thereafter. The following criteria were used to identify changes that were considered to be compatible with acute myocardial infarction or acute ischemic injury:

Infarction. Appearance of significant persistent Q waves or of QS deflections associated with changes in the S-T segment and with T waves.
Ischemic injury. (1) Flat S-T segment depression of greater than 2 mm. in left ventricular leads, lasting more than 48 hours, (2) deep T wave inversions persisting for more than 48 hours[13] (3) ventricular arrhythmias, such as ventricular tachycardia or ventricular fibrillation, and (4) absence of recent significant Q waves or QS deflections.

All records were reviewed by two observers who agreed upon the classification of the ECG. The following serum enzyme determinations were performed preoperatively and postoperatively on days 1, 2, 3, 6, and 10: serum glutamic oxalacetic transaminase (SGOT), lactic dehydrogenase (LDH), and creatine phosphokinase (CPK). Upper limits prior to operation were considered to be 40, 350, and 60 units, respectively. Standard analytical methods were employed.[7,8] Complete pre- and postoperative data on SGOT levels were available in 41 patients, data on LDH were available in 43 patients, and data on CPK were available in 21 patients. All patients had at least two determinations of all three serum enzymes in the first five postoperative days.

Information regarding clinical details and operative procedures was obtained from the patients' clinical records and from operative reports. Nearly all patients were observed personally by at least one of the authors.

Results

ECG changes. Signs of acute infarction or ischemic injury occurred in 22 patients (44 per cent). Acute infarction patterns were observed in 17 patients (34 per cent) of the total group, while changes compatible with ischemic injury alone were seen in 5 patients (10 per cent). Representative ECG's are illustrated in Figs. 1 and 2.

ECG's in the remaining 27 patients (56 per cent) exhibited no changes suggestive of infarction or ischemic injury. Changes in the S-T segments and T waves compatible with postoperative pericarditis and the appearance of atrial or ventricular premature beats were frequently observed, however.

Changes in serum enzymes. Analysis of the serum enzyme changes was performed by identifying the patients who exhibited a rise in enzymes above that level that might be expected to occur as a normal response to cardiopulmonary bypass surgery without the occurrence of myocardial infarction or ischemic myocardial injury. The levels selected were as follows: SGOT, 90 units; LDH, 900 units; and CPK, 200 units. The selection of these levels was based on experience in our laboratory and on data previously published by others.[4,10,11]

Elevation of SGOT levels exceeding 90 units occurred in 16 (32 per cent) of 50 patients. The highest levels were usually present on the first and second postoperative days with a subsequent gradual decline. Abnormal levels were still frequently present on the fifth day.

Elevation of LDH levels exceeding 900

Ischemic myocardial injury during coronary artery surgery

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Acute myocardial infarction, a frequent complication of surgery for coronary artery disease, is probably the major cause of operative death.[1] Nonfatal infarction occurs in 9 to 20 per cent of patients and is a probable cause of postoperative complications such as shock, left ventricular failure, and cardiac arrhythmias.[1-4] Myocardial infarction during the course of coronary artery surgery may have long term effects upon cardiac function and angina pectoris.[4-6]

Few systematic studies have been made of this important problem despite the increasing popularity of newer methods of bypassing local obstruction lesions in major coronary arteries.

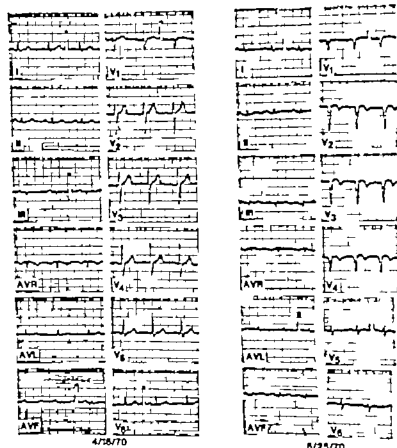
It is the purpose of the present study to further examine the incidence of myocardial infarction during coronary artery surgery with particular reference to the electrocardiogram (ECG) and serum enzyme levels.

Materials and methods

An initial evaluation was carried out on a consecutive series of 50 patients operated upon at the Palo Alto Veterans Administration Hospital (PAVAH) and at the Stanford Medical Center from March 8, 1966, to May 19, 1970, utilizing the same surgical technique. Surgical procedures consisted of (1) internal mammary artery implantation (IMI), (2) saphenous vein bypass graft, and (3) miscellaneous operations to increase coronary flow. The operative technique for IMI has been previously described.[1] The essential features of the operative technique employed for saphenous vein bypass grafts consist of (1) whole blood primed cardiopulmonary bypass with high pressure–high flow perfusion, (2) electrical fibrillation of the heart, (3) local hypothermia during anastomosis using the pericardial well technique, and (4) cannulation of both venae cavae and the ascending aorta.

A total of 50 patients was studied, 45 of whom were men and 5 of whom were women. The mean age was 50 years (the range was 35 to 69 years). Surgery was performed for the relief of incapacitating angina or (in 6 patients) for the alleviation of repeated bouts of acute ischemic pain

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. 2 ECG before and 5 weeks after single saphenous vein graft to the left axis deviation (LAD) coronary ery ECG signs of acute anteroseptal infarction appeared on the first postoperative day

Discussion

Electrocardiogram. Electrocardiographic idence of acute myocardial infarction llowing double internal mammary implants was observed by Dietrich and associates[3] in 11 (27.5 per cent) of 40 patients. gnificant serum enzyme rises occurred in 9 patients (48 per cent) Shirey Proudfit, nd Sones studied 125 patients who had urgery for coronary artery disease. Eighty ne had internal mammary implants and 16 atients (20 per cent) had postoperative vidence of acute infarction Greenberg and olleagues stud ed 40 patients who had imilar operations seven patients (17 6 per ent) had postoperative infarcts. These tudies report a lower ncidence of infarc ion than the 34 per cent observed in the resent study

Serum enzymes. It is well known that ardiac surgery will result in an increase in serum enzymes during the immediate postoperative period An evaluation has been made of serum enzyme levels follow ing cardiopulmonary bypass surgery in patients without coronary disease.[11] The following values were considered to represent the upper expected limits in patients who exhibited neither ECG nor clinical evidence of postoperative infarction or ischemia SGOT 90 units, and LDH 900 units. CPK levels were found to correlate poorly with evidence of infarction or ischemia.

Dietrich and colleagues[3] in their study of 40 patients reported that SGOT levels of less than 100 units were observed in patients without ECG evidence of post operative infarction. In the study by Shirey and co-workers of 125 patients 97 patients without ECG evidence of infarc tion had postoperative SGOT levels of less

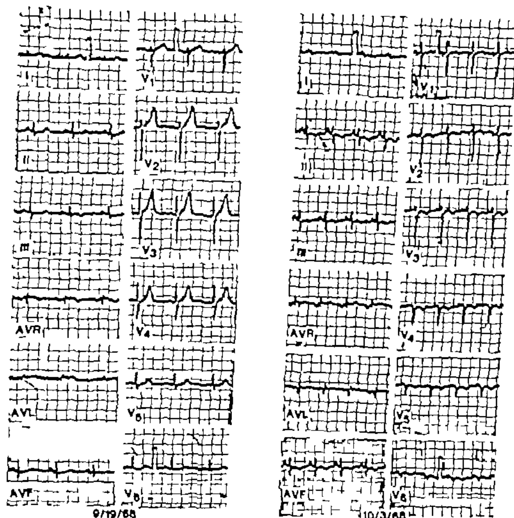


Fig. 1. ECG before and 13 days after a double internal mammary artery implantation (IMI) for angina pectoris, showing the appearance of anterolateral wall infarction.

units occurred in 12 (24 per cent) of 50 patients. The highest levels occurred on the third postoperative day with only a slight decrease by the fifth day.

Elevation of CPK levels exceeding 200 units occurred in 23 (46 per cent) of 50 patients. The highest level occurred on the first postoperative day with a rapid fall so that levels below 150 units were usually present by the fifth day. The data are summarized in Figs. 3, 4, and 5.

Mean serum enzyme levels in patients who did not exhibit ECG evidence of ischemic injury or infarction are illustrated in Figs. 3, 4, and 5. One standard deviation above the highest mean postoperative value in this group was 69 units for SGOT, 720 units for LDH, and 381 units for CPK.

Correlation of ECG changes and serum enzymes. Of the 22 patients with ECG evidence of ischemia or infarction, 11 (50 per cent) had abnormal SGOT levels, 12 (55 per cent) had abnormal LDH levels, and 6 (27 per cent) had abnormal CPK levels.

A reverse correlation study revealed that of 16 patients with SGOT levels exceeding 90 units, 11 (69 per cent) had ECG abnormalities. Of 12 patients with LDH levels exceeding 900 units, 12 (100 per cent) had ECG abnormalities. In 23 patients with CPK levels over 200 units, 14 (60 per cent) had ECG abnormalities. These data are summarized in Tables I and Ia.

ECG, serum enzyme changes, and clinical correlation. No relationship could be established between the total duration of surgery, bypass time, or aortic cross-clamp time and the incidence of postoperative ECG or serum enzyme changes. Patients with prior myocardial infarction did not have a higher incidence of postoperative abnormalities than patients who did not have evidence of myocardial infarction prior to surgery.

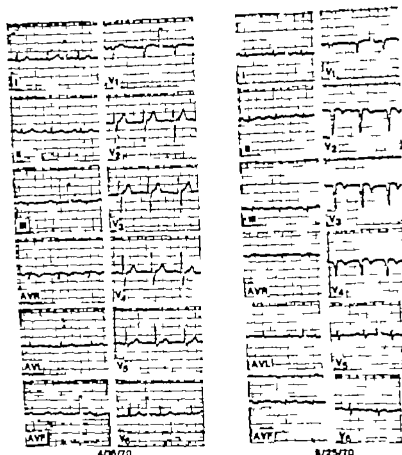


Fig. 2 ECG before and 5 weeks after single saphenous vein graft to the left axis deviation (LAD) coronary artery. ECG signs of acute anteroseptal infarction appeared on the first postoperative day.

Discussion

Electrocardiogram. Electrocardiographic evidence of acute myocardial infarction following double internal mammary implants was observed by Dietrich and associates[8] in 11 (27.5 per cent) of 40 patients. Significant serum enzyme rises occurred in 19 patients (48 per cent). Shirey, Proudfit, and Sones studied 125 patients who had surgery for coronary artery disease. Eighty one had internal mammary implants and 16 patients (20 per cent) had postoperative evidence of acute infarction. Greenberg and colleagues studied 40 patients who had similar operations; seven patients (17.6 per cent) had postoperative infarcts. These studies report a lower incidence of infarction than the 34 per cent observed in the present study.

Serum enzymes. It is well known that cardiac surgery will result in an increase in serum enzymes during the immediate postoperative period. An evaluation has been made of serum enzyme levels following cardiopulmonary bypass surgery in patients without coronary disease.[11] The following values were considered to represent the upper expected limits in patients who exhibited neither ECG nor clinical evidence of postoperative infarction or ischemia: SGOT, 90 units, and LDH, 900 units. CPK levels were found to correlate poorly with evidence of infarction or ischemia.

Dietrich and colleagues[8] in their study of 40 patients reported that SGOT levels of less than 100 units were observed in patients without ECG evidence of postoperative infarction. In the study by Shirey and co-workers of 125 patients, 97 patients without ECG evidence of infarction had postoperative SGOT levels of less

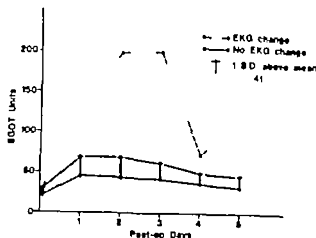


Fig. 3. Mean serum SGOT level in patients without evidence of ischemic injury or infarction, compared with mean level of patients with ECG changes. The shaded area indicates one standard deviation above the mean.

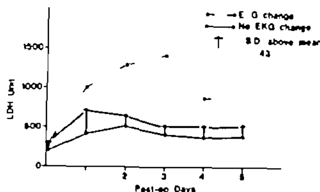


Fig. 4. Mean LDH level in patients without evidence of ischemic injury or infarction compared with mean levels of patients with ECG changes. The shaded area indicates one standard deviation above the mean.

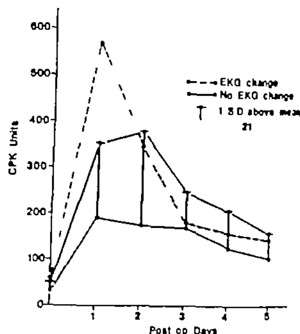


Fig. 5. Mean CPK levels in patients without evidence of ischemic injury or infarction compared with mean levels of patients with ECG changes. The shaded area indicates one standard deviation above the mean.

than 110 units. In patients with post operative infarcts, the SGOT level was greater than 109 units in all but one case. Greenberg and associates[4] reported similar data. Eleven of 17 patients with SGOT levels greater than 100 units had ECG evidence of infarction while no infarction patterns were seen in patients with SGOT levels of less than 100 units.

The present study supports the observations of these authors that elevated SGOT levels correlate with ECG evidence of postoperative myocardial infarction. However, the data reported in this paper indicate a higher total incidence of ECG evidence of postoperative infarction following coronary surgery. In addition, approximately 50 per cent with ECG signs of infarction did not have significant elevations of SGOT or LDH.

While both Dietrich and Shirey noted a poor correlation between LDH levels and ECG signs of infarction, this was not observed in the present study, where all 12 patients with LDH levels exceeding 900 units had ECG evidence of infarction or ischemia. CPK values correlated poorly with ECG changes.

In another study from this laboratory ECG changes and serum enzyme elevations were evaluated following cardiopulmonary bypass surgery in patients without coronary disease. Ischemic changes without infarction were more commonly observed following bypass surgery (30 per cent versus 10 per cent), while following coronary surgery infarction patterns were more frequent (34 per cent versus 7 per cent). Serum enzyme elevations were comparable in both groups (Table II).

Clinical complications. Myocardial infarction is the most important cause of hospital death following internal mammary implants or coronary artery surgery. The seven hospital deaths in Vineberg and Walker's[12] series of 128 patients were all due to myocardial infarction. Favaloro and associates[3] reported 63 infarctions in 675 patients who had internal mammary implantation, an incidence of 9.3 per cent.

Table I. Serum enzyme values in patients without ECG changes

Variable	Preoperative	Postoperative days				
		1	*2*	*3*	*4*	*5*
SGOT (= 24)						
Mean	20	43	44	42	36	31
S.D	8	44	25	21	13	14
LDH (= 24)						
Mean	204	432	513	406	370	383
S.D	93	298	149	123	131	149
CPK (n = 13)						
Mean	24	188	176	160	127	103
S.D	15	164	203	93	84	54

*Only patients with complete enzyme studies are included.

Table II. Serum enzyme values in patients exhibiting infarction or ischemia

Variable	Preoperative	Postoperative days				
		1		*3*	*4*	*5*
SGOT (= 17)						
Mean	25	131	198	200	73	120
S.D	10	92	417	490	48	196
LDH (n = 19)						
Mean	277	986	1 315	1 429	863	893
S.D	90	648	1 504	2 092	414	727
CPK (= 8)						
Mean	33	572	344	175	163	149
S.D	17	362	309	153	101	42

*Only patients with complete enzyme studies are included.

Sheldon and co-workers[13] reported that 9 out of 100 patients had myocardial infarction during venous autograft shunt operations. The mortality rate is higher in patients with severe coronary disease and angina at rest.[14,15]

In the present study two patients died and acute infarction was demonstrated at autopsy seven patients with postoperative infarction had serious nonfatal postoperative complications including cardiac arrhythmias, shock, and left ventricular failure.

Late effects of postoperative infarction. In all patients who had postoperative QRS abnormalities compatible with acute infarction the abnormalities persisted for a period of several weeks to several years after surgery. When infarction is extensive and leads to persistent left ventricular dysfunction, relief of angina may occur.

In a preliminary analysis of the late results of coronary artery surgery in 40 patients, 11 patients were observed who had experienced complete relief of angina for at least one year following operation. Five of these patients had experienced myocardial infarction during surgery and in two of these patients it is possible that myocardial infarction was the mechanism of pain relief. One of these patients is described in the following paragraph.

Table II. Per cent incidence of ischemic changes, acute infarction, and abnormal serum enzyme levels following cardiopulmonary bypass surgery and coronary artery disease surgery

Variable	Ischemic changes	Myocardial infarction	No ECG change	SGOT > 90	LDH > 900	CPK > 200
CPBS (n = 60)	30	7	63	3	3	40
CAS (n = 50)	10	34	56	3	7	45

Abbreviations: CPBS = cardiopulmonary bypass surgery; CAS = coronary artery surgery.

Case report

J. D., a 41 year-old security guard, had angina pectoris of increasing severity for 3 years. The episodes occurred during mild effort and he had experienced as many as 12 to 14 attacks per day despite marked restriction of activity. There was no prior history of infarction. His blood pressure was 1 0/80 and his physical examination was normal. The resting ECG showed only minor T wave abnormalities. A treadmill test was positive with 2 mm. flat S-T depression during exercise at a heart rate of 120 per minute. Coronary arteriography demonstrated a complete occlusion of the right coronary artery 1 cm. from its origin. Severe diffuse disease was present in the left circumflex artery but only mild disease was present in the left anterior descending branch. On Sept. 20, 1968, a double internal mammary implant was performed. Following operation an acute anterior myocardial infarct occurred with recurrent episodes of ventricular tachycardia requiring DC cardioversion. The SGOT rose to 252 units. The patient's ECG is illustrated in Fig. 1. Following his convalescence he noted a marked decrease in his episodes of angina. He returned to full time work and now experiences only 1 to 2 episodes of mild angina per week which are quickly relieved by nitroglycerine. On April 28, 1970, he re-entered the hospital for follow up study. A selective arteriogram demonstrated occlusion of one internal mammary artery near its origin. The other internal mammary artery sent a few small branches to the myocardium but no contrast medium appeared in either the coronary vessels or the coronary sinus. The coronary arteries were unchanged. The ECG continues to show a pattern consistent with a healed anterior myocardial infarct.

Shirey and co-workers[8] performed left ventricular angiograms in 125 patients from 3 to 22 months after internal mammary implantation. In six of eight patients with ECG evidence of acute myocardial infarction following surgery, there was angiographic evidence of impaired contractility of the anterior and posterior diaphragmatic or apical segments of the left ventricle which was not present on the preoperative angiogram. In five of these patients, the coronary arteriogram was not changed from the preoperative study. Greenberg and colleagues[4] reported similar observations.

Thus an important aspect of nonfatal myocardial infarction following coronary artery surgery is the resulting impaired left ventricular contractility. The effect of these complications upon the mechanism of relief of angina in some patients requires further study.

Value of serum enzyme studies. Routine postoperative evaluation of serum enzymes in patients undergoing coronary artery surgery may be a valuable method of detecting acute ischemic myocardial damage and evaluating the effectiveness of myocardial protection during cardiopulmonary bypass.

In the present study it should be noted that 62 per cent of patients had internal mammary implants and 34 per cent had saphenous vein bypass grafts. The number of patients studied was too small to determine if myocardial infarction was more frequent in the internal mammary implant group. In addition, the bypass group represents our initial experience with this operation. It may well be possible that with further operative experience the incidence of myocardial infarction will be lower in subsequent bypass operations.

Summary

ECG's and serum levels of SGOT, LDH, and CPK were examined during the postoperative period in 50 patients with angina pectoris who had myocardial revascularization procedures. ECG signs of acute myocardial infarction appeared in 34 per cent and changes compatible with acute ischemic injury were seen in 10 per cent. Elevation of SGOT exceeding 90 units occurred in

32 per cent of 30 patients, and LDH levels over 900 units occurred in 24 per cent. In patients with ECG evidence of post operative infarction or ischemia 50 per cent had abnormal SGOT levels and 55 per cent had abnormal LDH levels. In 16 patients with SGOT levels exceeding 90 units 69 per cent had ECG evidence of acute infarc tion or ischemia. Two patients died follow ing surgery and acute myocardial infarction was demonstrated in both at autopsy Relief of angina occurred in one patient who developed a myocardial infarct fol lowing internal mammary implantation A follow-up angiogram revealed no effective communication of the implant with myo cardial vessels. Acute myocardial infarc tion is a frequent complication of coronary artery surgery as determined by serial ECGs. In this study approximately 50 per cent of these patients had diagnostic elevations of SGOT or LDH

Addendum

Since this paper was prepared 30 addi tional consecutive patients have been stud ied All had saphenous vein bypass opera tions without implants. ECG evidence of infarction appeared in 3 (10 per cent) and acute ischemic injury patterns occurred in 10 (33 per cent) Elevation of SGOT levels exceeding 90 units occurred in 12 (40 per cent) and LDH levels over 900 units oc curred in 10 (33 per cent) One patient died of acute myocardial infarction follow ing surgery

These data indicate a lower incidence of myocardial infarction with saphenous vein bypass surgery than with internal mam mary implants. The incidence of abnormal enzyme elevations is similar however

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Experimental and laboratory reports

Cardiocirculatory responses to exercise Physiologic study by noninvasive techniques

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Satisfactory assessments of myocardial function by timing the phases of the cardiac cycle during rest have been well demonstrated[1,2] Exercise electrocardiography in an attempt to meet the need for further cardiac evaluation has also become increasingly popular as a diagnostic and screening procedure[3-5] but it records only electrical activity and thus remains limited in the amount of information it can offer The assessment of cardiocirculatory adaptation to stress by measurements of the phases of systole appears to be an important additional diagnostic and screening procedure

Systematic studies of the independent effects of variables such as stroke volume heart rate and aortic pressure on ejection time and the pre-ejection period have been carried out on dogs[6-9] and on patients with complete heart block and atrioventricular dissociation[10] as well as in hospital normals and hypertensives.[11] Studies have also been conducted to determine cardiocirculatory responses to exercise[12-15] The results of these studies however have led to a variety of conclusions. Harley and associates[10] reported a close direct relationship between stroke volume and ejection time and further stated that heart rate bears a weak but independent relationship to duration of ejection Jones and Foster[14] on the other hand reported that heart rate is the most influential factor governing the time of left ventricular ejection While there was general agreement that heart rate does bear an inverse relationship to ejection time Rowell s work[13] suggests that during light stress (HR = 100 and maximal minute volume of oxygen consumption = 28 per cent) left ventricular ejection time might not decrease despite an increase in heart rate from rest to exercise

It should be noted that these results are drawn from a wide variety of experimental designs. Subjects ranged from normal males

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to hospital "normals," hypertensives, and patients with complete heart block these human responses were further compared to results derived from examining anesthetized dogs and dog heart preparations. Moreover studies with pooled data were compared to studies which utilized repeated measures in the same subjects undergoing different interventions. Certain investigations necessarily involved systematic analysis of selected variables (e.g the effect of stroke volume on isovolumic contraction time and ejection time while heart rate and aortic pressure were held constant) while others used interventions which may well have affected both heart rate and stroke volume simultaneously Some data were determined in supine subjects while other studies utilized an upright patient position Finally results for exercise were based on challenges which varied from light to maximal stress.

The purpose of this study was to determine the normal cardiocirculatory response to rate-standardized, moderately heavy stress when performed in the upright sitting position These responses were assessed by measuring the isovolumic contraction time (IVCT) pre-ejection period (PEP) left ventricular ejection time (LVET) and the pulse transmission time (PTT) These noninvasive techniques were employed to minimize physical and psychological hazards and to provide an opportunity to repeat the procedures as often as needed.

Material and methods

Ten healthy normally active volunteers, ages 22 to 37 were studied. The following screening procedures were normal in each (1) medical history (2) physical examination, (3) 12 lead electrocardiogram and (4) chest X ray None of the subjects were obese none were trained athletes, and none were taking medication

Subjects were asked to assume a comfortable sitting position on the bicycle ergometer Two General Electric or Derma Circ disposable electrocardiographic monitoring electrodes were pasted over the subject's sternum one electrode was applied over the manubrium and the other over the caudal aspect of the body of the sternum. The wires from these electrodes were attached to the right arm and left arm ECG leads respectively The right leg electrode was strapped around the subject's wrist to act as a ground. The leads were then connected to the "Lead I" portion of the ECG channel.

Heart sounds were recorded at the apex with an HP model A/B contact sensor secured by a rubber belt. Nominal filter frequency was set at 50 Hz A Sanborn piezoelectric crystal and funnel were used to register the carotid pulse over the maximal external point of pulsation of the right carotid artery Filter cutoffs were set at 20 and at 0.15 Hz. The ECG PCG and carotid pulse tracings were recorded on an eight channel Hewlett Packard Sanborn oscillograph No. 568-100 A.

A Collins bicycle ergometer and cardiotachometric controller were used to provide for physiologically paced ergometry A Sanborn earpiece plethysmograph Model 780-16 was used to measure heart rate through the pinna of the subject's ear The earpiece was further secured by a headband with a side clip through which the wire could be passed and supported

Resting heart rate was observed (without the subject's knowledge) on the "True Heart Rate" meter of the cardiotachometric controller until it stabilized Control recordings were then taken. The subject was then instructed to pedal at a constant but *comfortable* rate (60 to 80 revolutions per minute as evidenced on the "Pedal Speed" meter of the Pedal-Mode Ergometer) A minimum of seven additional sets of measurements was made on each of the 10 subjects. This involved ECG PCG and carotid pulse tracings at the end of each minute of exercise during the loading period (i.e heart rate less than but approaching 150 beats per minute) and at the end of each five minutes of exercise after attaining the pre-set heart rate of 150 beats per minute.

The following points were designated on the tracings (Fig 1) (1) the q wave of the ECG (q) (2) the first rapid (mitral) component of the first heart sound (I_M) (3) the first rapid (aortic) component of the second heart sound (II_A) (4) the carotid upstroke (CAR_u) and (5) the carotid incisura (CAR_{in}) The onset of the q wave was designated zero time for each beat.

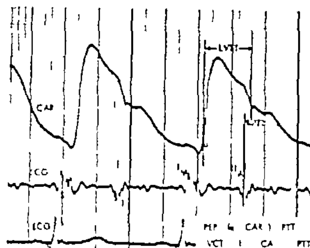


Fig 1 Simultaneous recording of the electrocardiogram (ECG) phonocardiogram (PCG) and carotid pulse tracing (CAR) Methods for measuring pre-ejection period (PEP) isovolumic contraction time (IVCT) left ventricular ejection time (LVET) and pulse transmission time (PTT) are indicated See text.

The timing from q to each of the four designated points was determined in five beats during the control period and in five beats during each minute of exercise thereafter Mean values for the control period and for each minute of exercise were then determined The following calculations were made from the measurements (Fig 1)

(1) Pre Ejection Period (PEP)
PEP = q to CAR minus PTT*
(2) Isovolumic Contraction Time (IVCT)
IVCT = I_M to Ej*
(3) Left Ventricular Ejection Time (LVET)
LVET = CAR_u to CAR_{in}
(4) Corrected Ejection Time

$$\text{Corrected Ejection Time} = \frac{\text{LVET}}{\sqrt{\text{R R interval}}}$$

(5) Pulse Transmission Time (PTT)
PTT = II_A to CAR_{in}

A randomized block design was used to determine whether a statistically significant difference (or differences) existed at the 0 01 level between any of these periods. When such differences were found (i e. F values were obtained which exceeded the appropriate table values) Duncan s New Multiple Range Test was applied to determine the exact location of differences between values during rest and values during each particular minute of exercise.

Results

The loading period designated in this study by the small letters a through h (time when heart rate was less than but approaching the largest figure of 150 beats per minute) varied from two to eight minutes for the different subjects. Because an unequal number of subjects (less than 10) were exercising during minutes c through h of the loading period these minutes were not included in the statistical analysis of the data Hence the analysis of variance included the control period (sitting at rest) the first two minutes of loading and each of the five minutes with heart rate at the preset pace of 150 beats per minute

Results are summarized in Table I and are illustrated in Figs. 2 and 3 The periods presented along the abscissa are as follows Control = sitting resting value a and b = first two minutes of exercise during the loading period and 1 2 3 4 and 5 = five minutes of exercise at the preset heart rate of 150 beats per minute Results during any periods underscored by the same line did not differ significantly Periods along the abscissa not underscored by the same line did differ significantly ($p < 0\ 01$)

Pre Ejection Period (PEP) The mean values and standard errors for PEP are illustrated in Fig 2 A very large decrease in PEP (127 to 79 6 msec) occurred between rest and the first minute of exercise ($p < 0\ 01$) A further decrease of 13 6 msec. ($p < 0\ 01$) occurred between the loading period and the five minutes of exercise with heart rate at 150 beats per minute. The Duncan Test showed no statistical difference between minutes a and b (PEP = 79 6 and 72 6 msec respectively) at the 0 01 level nor was such a difference indicated between the five minutes of exercise at the preset heart rate of 150 beats per minute (PEP range of 60 4 to 63 6 msec)

Isovolumic Contraction Time (IVCT) The mean results and standard errors for IVCT are illustrated In Fig 2 It is clear that the changes in IVCT were very similar to the decreases noted for PEP IVCT decreased markedly from 79 6 to 30 4 msec. ($p < 0\ 01$) between the control value and

*The pre-ejection period (PEP) is the time from q to the calculated onset of ejection; time of onset of ejection is also designated Ej

Table I. Mean values and standard errors for the systolic intervals during rest and exercise

Variables	Intervals									
	Control		*b*		*d*	*1*	*2*	*3*	*4*	*5*
Heart rate (beats/min.)										
Mean	82.4	113.3	120.6	120.9	137.1	150.5	151.1	150.2	149.7	150.4
S.E.	±3.26	±5.47	±3.85	±4.04	—	±0.27	±1.02	±0. 1	±0.62	±0.45
Pre-Ejection Period (msec.)										
Mean	127.0	79.0	72.0	64.7	63.7	60.4	62.2	63.6	63.2	63.2
S.E.	±5.6	±3.54	±3.13	±2.43	—	±2.90	± 10	±3.30	±2.33	±3.63
Isovolumic Contraction Time (msec.)										
Mean	79.0	30.4	26.6	18.4	19.7	20.6	20.8	22.4	22.4	23.0
S.E.	±8.06	±3.16	±3.10	±3.03	—	±2.39	±2. 5	±2.64	± 63	± 91
Pre-Isovolumic Contraction Time – [q – I_M] (msec.)										
Mean	43.0	49.2	46.0	46.2	44.0	39.5	41.4	41.2	40.8	40
S.E.	±4.23	±3.05	±3.82	±2.66	—	±2.80	±3.73	±3.01	±2.62	±2.85
Pulse Transmission Time (msec.)										
Mean	37.0	37.2	35.4	35.8	34.6	33.4	36.2	35.2	37.4	36.8
S.E.	±2.18	±2.07	±2.06	±1.90	—	±2.0	±1.44	±1.47	±1.44	±2.30
Left Ventricular Ejection Time (msec.)										
Mean	225.2	228.6	230.8	214.9	205.1	151.8	150.6	177.8	175.8	174.0
S.E.	±4.20	±5.96	±6.33	±6.20	—	±4.07	±3.92	±4.14	±2.63	±3.33
Corrected Ejection Time*										
Mean	302.6	300.7	311.5	315.3	308.3	283.7	256.6	251.1	277.7	275.4
S.E.	±3.42	±4.90	±5.66	±7.16	—	±0.37	±6.03	±6.23	±4.70	±5.14
PEP/LVET										
Mean	0.563	0.340	0.329	0.302	0.311	0.323	0.348	0.300	0.361	0.367
S.E.	±0.023	±0.014	±0.014	±0.017	—	±0.017	±0.016	±0.021	±0.016	±0.024

Symbols: Control — during resting values; a-d — loading period with heart rate approaching but less than 150 beats per minute; 1-5 — exercise at pre-set heart rate of 150 beats per minute.

the first minute of exercise. This level was basically maintained throughout the entire exercise period (range 30.4 to 20.6 msec.). A small decrease (mean difference = 6.7 msec.) in IVCT was noted between the loading period and the five minutes of exercise with heart rate at 150 beats per minute, but this difference did not represent a statistically significant change (Fig. 2). Hence the results show that the control period differed from all minutes of exercise with $p < 0.01$ while no remarkable difference in IVCT existed between any of the minutes of exercise.

Pre-Isovolumic Period ($q-I_M$). An analysis of the variance was also applied to the pre-isovolumic contraction time (q wave to the mitral component of the first heart sound or $q-I_M$). The mean results and standard errors for this interval are illustrated in Fig. 2. The Duncan Test showed no statistical difference at the 0.01 level between the control value and minutes a and b of exercise ($q-I_M$ = 48.0 and 49.2 msec. respectively). Furthermore no such differences were found between any of the five minutes of exercise with the heart rate at 150 beats per minute ($q-I_M$ = 41.4 to 39.8 msec.). However $q-I_M$ times during these last five minutes of exercise were shown to differ significantly ($p < 0.01$) from both the control and loading period values.

Left Ventricular Ejection Time (LVET). The results for LVET are illustrated in Fig. 3. The mean values for the 10 subjects indicate a slight increase in LVET (225.2 to 228.6 msec.) from control values to the first minute of exercise during the loading

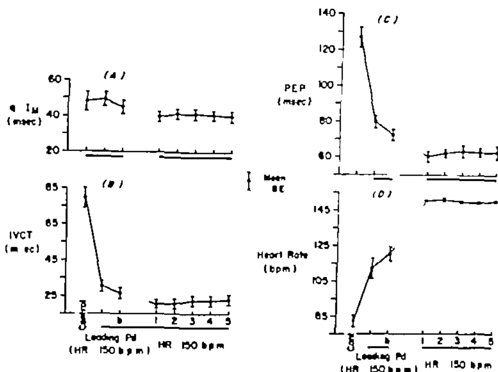


Fig. 2. Mean values and standard errors for (A) $q - I_M$ or pre-isovolumic contraction time (B) isovolumic contraction time (C) pre-ejection period and (D) heart rate. Control = sitting resting value. a and b = loading period of exercise when heart rate is less than but approaching 150 beats per min. and 1 2 3 4 and 5 = exercise with heart rate equal to 150 beats per min. *Tests of significance:* Periods underscored by the same line do not differ significantly ($p \geq 0.01$). Any periods not underscored by the same line differ significantly with $p < 0.01$.

period. Application of the Duncan Test to these values indicated that this change did not represent a statistically significant difference at the 0.01 level. A large and significant decrease in LVET ($p < 0.01$) did occur during exercise with a tendency to level off during the entire exercise period while the heart rate was held at 150 beats per minute. No statistically significant differences were found between any of the five minutes with the heart rate at 150 (LVET = 170.0 to 174.8 msec.).

Corrected Ejection Time. When LVET was corrected for heart rate the increase from rest to exercise (262.6 to 309.7 msec.) became statistically significant with $p < 0.01$ (Fig. 3). A moderately large decrease occurred in the corrected ejection time (mean difference 27.5 msec.) $p < 0.01$ between the loading period and the exercise period with heart rate at 150 beats per minute. The corrected ejection time showed a gradual decrease throughout this latter five minute period. The values for minutes 1 and 2 (292.7 and 286.6 msec. respectively) were significantly higher ($p < 0.01$) than those for minutes 4 and 5 (277.7 and 275.4 msec. respectively). Despite the large decrease in corrected ejection time from the loading period to the exercise period with heart rate at 150 beats per minute, values for this latter period still remained significantly higher ($p < 0.01$) than the control value.

PEP/LVET Ratio. In order to further assess the myocardial responses to stress the ratio of PEP to LVET was calculated. Mean results and standard errors are illustrated in Fig. 3. The analysis of variance applied to the ratio for the different periods under study showed that no statistically significant differences existed between any of the minutes of exercise (PEP/LVET during exercise = 0.328 to 0.367). These values, however, did differ ($p < 0.01$) from the control value of 0.563.

Pulse Transmission Time (PTT). The mean results and standard errors for PTT are illustrated in Fig. 3. The graph shows minor fluctuations in PTT during the control and exercise periods (PTT range = 38.4 to 35.2 msec.). The F value obtained (0.916) was too low to reject the null hypothesis at the 0.05 level however. There-

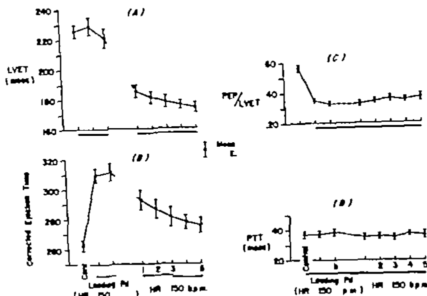


Fig. 3 Mean values and standard errors (*A*) left ventricular ejection time, (*B*) corrected ejection time (*C*) ratio of pre-ejection period to left ventricular ejection time, and (*D*) pulse transmission time. Control = sitting resting value and *b* = loading period of exercise when heart rate is less than but approaching 150 beats per min. and *1 2, 3 4* and *5* = exercise with heart rate equal to 150 beats per min. *Tests of significance*: Periods underscored by the same line do not differ significantly ($p > 0.01$). Any periods not underscored by the same line differ significantly with $p < 0.01$.

fore the results indicate that no real differences exist between the control value and any of the exercise values.

Heart Rate. An analysis of the variance was also applied to the values for heart rate as determined by the actual tracings for each subject during the control period and each minute of exercise The mean values and standard errors of these values are illustrated in Fig 2 Application of the Duncan Test showed that the control heart rate (82 4 beats per minute) was significantly lower ($p < 0.01$) than the heart rates achieved during any of the minutes of exercise. Minutes a and b of the loading period (HR = 112.3 and 120 6, respectively) did not differ from one another but both were statistically different ($p < 0.01$) from the control HR and the five minutes of exercise at the pre-set heart rate of 150 No difference ($p > 0.01$) was found between any of the five minutes of exercise during which time the heart rate was, in fact, supposed to coincide with the preset heart rate of 150 beats per minute. The graph of heart rate in Fig 2 demonstrates this very close proximity of the true heart rate to that of the preset rate (i.e., the highest mean value is 151 1 ± 1 02 beats per minute and the lowest mean value is 149 7 ± 0 62 beats per minute)

Discussion

The uniform response to stress by all subjects indicates that noninvasive techniques are an appropriate means for determining cardiac response during exercise.

Pre Ejection Period and Isovolumic Contraction Time The PEP is comprised of the pre-isovolumic time ($q-I_M$) and the isovolumic contraction time (IVCT) The results showed that there is a decrease in $q-I_M$ with exercise, eliciting a heart rate of 150 beats per minute as compared to resting values and exercise at lower heart rates (112 to 120 beats per minute) Factors which influence $q-I_M$ duration include depolarization times intramyocardial conduction, contractile responsiveness of the myocardium, and the rate of rise of myocardial tension Shortening of $q-I_M$ with exercise at a heart rate of 150 beats per minute indicates that such a challenge elicits a more rapid completion of the son

of these processes without distinguishing among them However it is likely that there was an acceleration of the contractile rather than the electrical components of this interval

IVCT showed a large decrease with exercise The great similarity between the curves of IVCT and PEP (while $q-I_M$ changed minimally by comparison) would indicate that the changes in PEP with exercise are primarily due to changes in IVCT Isovolumic contraction time reflects the initial velocity of myocardial contraction[12] and the rate of increase in ventricular pressure (dp dt) [19] Thus the decrease in IVCT implies that exercise increases either myocardial contractile speed the rate of rise of intraventricular pressure or both Furthermore as demonstrated by the data the major part of this adaptation occurs within the first minute of exercise i e at relatively low stress as measured by heart rate Goldstein and associates[11] indicated that increased adrenergic activity results in a decreased IVCT Since exercise facilitates adrenergic activity [20] this inotropic influence might well account for part of the decrease in IVCT demonstrated in this study Venous return also increases with exercise [21] a factor which will also effect a decrease in IVCT [9] Wallace and his colleagues[9] further demonstrated that decreased IVCT can be associated with increased stroke volume Thus, the response of the isovolumic contraction period was entirely consistent with other physiologic responses to exercise

The techniques employed in this study were not capable of yielding direct measurements regarding stroke volume However Åstrand[22] demonstrated a consistent increase in stroke volume from rest to exercise in the sitting position His study showed that maximal (or nearly maximal) stroke volumes were achieved by the time the heart rate reached 110 beats per minute Thereafter the stroke volume levelled off with no tendency to decrease even when maximal work was performed The assumption can therefore be made that an increase in stroke volume occurred during the first minute of exercise with a tendency to level off during the remaining minutes of exercise. Data in the present study show an initial increase in heart rate followed by a steady state at the programmed heart rate of 150 beats per minute for the last five minutes of exercise Both of these factors—stroke volume and heart rate—have been shown to affect PEP inversely [19] The data from the current study demonstrated that when heart rate and presumably stroke volume were both altered simultaneously a decrease in PEI and IVCT ensued It is of interest that the greatest decrease in PEP occurred during the first minute of exercise (mean HR = 112 beats per minute) which would be the period during which the greatest increase in stroke volume would occur [22] Changes in PEP thereafter are much smaller while presumably only the heart rate is increasing This suggests (1) that while the isolated effect of increasing either heart rate or stroke volume is to decrease PEP [19] the combined effects of increasing these two parameters together may have a greater effect than that achieved by increasing either one independently and (2) that the changes became smaller because a minimum or floor value for PEP was approached or reached Moreover when heart rate reaches a steady state at 150 beats per minute and stroke volume is more or less constant [21,22] there are no changes in PEP (nor in $q-I_M$ or IVCT) Thus exercise elicits a marked decrease in the duration of the pre-ejectional phases (mainly the IVCT) implying increased velocity of contraction Furthermore, the major adaptation to the increased demands occurred within the first minute of exercise with tendencies to level off and remain constant when steady state heart rate was achieved

Left Ventricular Ejection Time As previously mentioned conclusions differ regarding the effects on ejection time of factors such as stroke volume and heart rate. The LVET in this study showed only a very slight (and not statistically significant) increase from rest to the first minute of exercise Thereafter the LVET dropped significantly below the resting value, then leveled off during steady-state heart rate at 150 beats per minute There appear to be several implications of these changes. Since the first minute of exercise was at a mean rate of 112 beats per minute this stability of LVET is consistent with the work of Rowell and associates,[18] which

suggests that light exercise eliciting heart rates around 110 beats per minute does not appear to effect any remarkable change in ejection time while more severe stresses will result in observable decreases in LVET Certain effects of changes in stroke volume and heart rate or ejection time can account at least in part, for this observation Åstrand [n] as well as Chapman and associates,[n] demonstrated a marked increase in stroke volume during initial phases of upright exercise with a tendency to level off thereafter On this basis it appears that the period of slightly increased LVET among subjects in the current study corresponds to the period during which stroke volume was also undergoing its largest increase (despite the increase in heart rate) When heart rate continued to increase, then leveled off at 150 beats per minute, there was a reciprocal decrease and plateauing in LVET with presumably little change in stroke volume. Hence it appears that at least up to a heart rate of about 112 beats per minute increases in stroke volume with exercise may be sufficient to maintain or slightly increase ejection time and in turn override the inverse effect of heart rate on ejection time. Later when stroke volume presumably levels off and greater increases in heart rate occur the inverse relationship between heart rate and ejection time becomes apparent It should also be noted that Jones and Foster[1] considered heart rate to be the major determinant in the duration of ejection Their study however was based on supine (rather than upright) exercise. No evidence was given in their study that stroke volume increased with exercise. A more recent study by Jones and associates[n] showed that supine exercise does not, in fact, elicit any remarkable change in stroke volume Hence the poor correlation between stroke index and ejection time reported by Jones and his co-workers might well be due to the fact that their subjects did not significantly increase their stroke volumes.

Lombard and Cope [n] Wallace and colleagues, and Wiggers reported that ejection time bears a direct relationship to venous return. This conclusion was based on evidence derived from resting humans and from examining dog heart preparations. Despite the anticipated increased venous return [n] data in the current study indicate that, except for possibly the first minute of exertion either this relationship is not maintained during exercise or that other factors influencing LVET override the effect of increased venous return

Braunwald and associates indicated that decreased ejection time associated with increased heart rate at rest are accompanied by augmentation of the ejection rate Wildenthal and Mitchell[n] demonstrated this same compensatory action to occur with exercise. Therefore, despite the demonstrated decrease in LVET it is likely that the subjects further adapted to the increased circulatory demands by increasing the rate at which blood was ejected from the left ventricle

Corrected Ejection Time Evidence from this study is consistent with other findings and shows that the general tendency of ejection time is to vary inversely with heart rate (Figs. 2 and 3) Removing the influence of heart rate from LVET is not only valuable for intersubject comparisons, but during physiologic changes in the same subject, it should disclose the strong influence of changes in stroke volume In rate-correcting the LVET our data show a very large statistically significant increase in the corrected ejection time from rest to the first two minutes of exercise (Fig 3) Conceivably any increased venous return might contribute to such a rise in corrected ejection time by an increased stroke volume However the curve of the corrected ejection time does not follow the anticipated curves of either stroke volume or venous return[n,n] i e these two variables would be expected to remain near the level achieved during the first few minutes of exercise and would not be expected to decrease, as did the corrected ejection time from the loading period to the period of steady-state heart rate at 150 beats per minute This decrease in corrected ejection time which continued even during the steady-state heart rate period may reflect the influence of factors associated with an increased ejection rate Changes in neural myocardial or chemical factors might account for such a decrease.

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of these processes without distinguishing among them. However, it is likely that there was an acceleration of the contractile rather than the electrical components of this interval.

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LVET per beat is small compared to the increase in heart rate. Thus the total ejection time per minute actually increases. The present study clearly indicated such an increase with exercise.

PEP/LVET Ratio. Weissler and his associates[16] have advocated the use of the ratio of PEP to LVET for assessing cardiac function. They found that the construction of this ratio tends to minimize the variation of both factors with heart rate. Their study also demonstrated a close inverse relationship of PEP/LVET with both cardiac output and stroke volume. Our results demonstrated an early decrease in the ratio from rest to exercise, a decrease which remained level throughout the entire exercise period. This implies that PEP/LVET reflected the increased cardiac output during exercise. Since Weissler made his measurements on supine resting subjects, further clarification of the relationship between PEP/LVET and stroke volume and cardiac output during upright exercise is needed before such a conclusion is warranted.

Pulse Transmission Time. The pulse transmission time should depend primarily on the condition of the arterial wall. Jona (in Luisada)[17] as well as Schimmler[18] reported that increased rigidity of the artery results in decreased PTT. Such changes, however, usually occur over long periods of time and coincide with age and disease. While static conditions of the arterial wall (e.g., the amount of sclerosis) could not be changed by exercise, it seemed conceivable that vascular factors such as vasodilation or constriction or the rate of ejection might alter elasticity and thus affect PTT. The results of the study showed no changes in PTT from rest to exercise nor during any of the minutes of exercise. This would seem to indicate that (1) exercise does not affect the condition of the arterial wall, (2) any influences tending to increase PTT were cancelled by opposing conditions, or (3) any net changes were too small to be measured.

Summary

Noninvasive as compared to invasive procedures appear to offer a practical method of quantitating the myocardial response to stress in that these techniques are quickly and easily applied, offer unlimited chances for repetitive studies, present no intrinsic dangers for the subject, and potentially do not require the presence of a physician. The changes from rest to exercise were determined for certain phases of the cardiac cycle in ten healthy male subjects who underwent submaximal physiologically paced bicycle ergometry at a preset heart rate of 150 beats per minute. Electrocardiograms, phonocardiograms, and carotid pulse tracings were recorded during sitting rest, at the end of each minute of the loading period (period when the heart rate was less than but was approaching 150 beats per minute), and at the end of each of five minutes of exercise when the heart rate was held at 150 beats per minute.

The pre-ejection period and isovolumic contraction time decreased with exercise. Changes in left ventricular ejection time appeared to depend upon the severity or the duration of stress, i.e., LVET did not change during the first minute but decreased significantly thereafter. Ejection time corrected for rate increased during the initial minutes of exercise, then continually decreased despite an eventual five minute steady state in heart rate and a levelling off of PEP, IVCT, and LVET. Pulse transmission time did not change significantly. The increased velocity of contraction implied by decreases in IVCT and LVET associated with an improved ratio of PEP and LVET and increased ejection time per minute are consistent with the positive inotropic influence of exercise on the myocardium. The data obtained in this study and comparison of these results to those obtained by invasive methods indicate that noninvasive techniques when used in the manner suggested are appropriate means for detecting a variety of cardiocirculatory changes during exercise.

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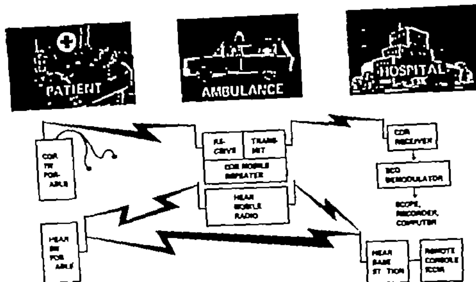


Fig. 1 Diagrammatic representation of the ECG telemetry system. The ECG telemetry originates from wher ever the patient is, and the signal is relayed via mobile repeater located in the ambulance, to the coronary care unit (CCU) Voice communications are maintained by remote console located in the CCU (See text.)

the ambulance and coronary care unit directly A HEAR console is located in the CCU where hospital personnel may con verse and relay instructions to ambulance personnel. Once the patient is transported to the ambulance the ECG signal is dis- connected from the 1 8-watt transmitter and inserted directly into the mobile re peater Voice communications are also maintained by the ambulance radio directly with the CCU

Since the patient s condition may re quire that he be transported to the nearest medical facility a miniaturized ECG (Sie mens Cardiostat T) is also linked to the mobile repeater allowing the ambulance personnel to record a rhythm strip. The diagnosis is provided by radio communica tion from the CCU physician-in-charge Thus, copies of abnormal rhythms may be presented to Emergency Room personnel who attend the patient at the receiving hospital

Upon arrival at the hospital the patient is reconnected to the hand-carried ECG transmitter This permits additional con tinuous monitoring while the patient is being transported from the ambulance to the receiving ward and while he is being con nected to the standard electrocardiograph. The hand-carried transmitter is powerful enough to insure a proper signal even while the patient is being transported in an elevator

Results

To date, 73 patients have been monitored by means of the ECG telemetry described above. Table I summarizes the arrhythmias observed in these patients.

Of the 73 patients 14 had myocardial infarction or acute coronary insufficiency and in these patients the following arrhyth mias were observed normal sinus rhythm 2 sinus tachycardia, 9 sinus bradycardia 1 premature atrial beats, 2 paroxysma atrial tachycardia, 1 premature ventricula beats, 5 ventricular tachycardia 1 asys tole, 2

Two case histories representative of th series are presented

Case 1 The patient, 75-year-old man, first note episodes of loss of consciousness in 1968. The syn cope became more frequent, often associated wit seizures. I August, 1970 pacemaker was im planted. After discharge from the hospital he co tinued to experience chest pain, and one episode syncope occurred in association with loss of mem ory However rhythm strips recorded during follo up demonstrated normally functioning pacemak I October 1970, while in his ninth floor office, developed severe palpitations, chest pain, a dyspnea. He summoned medical assistance and o of our ambulances arrived on the scene within minutes. Fig 3 shows the electrocardiogram tra mitted from the patient office. The pacemaker

Continuous prehospitalization monitoring of cardiac rhythm

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Recent reports[1-3] have emphasized that 40 to 60 per cent of deaths due to myocardial infarction occur within the first hour after onset of symptoms. These statistics draw attention to the need for improved methods of delivering medical care to the patient who suffers a myocardial infarction To meet this need the mobile coronary care unit (CCU) has been devised However the cost of installation of such a unit and personnel requirements prohibits the majority of hospitals and medical centers from maintaining such a unit.

Studies from these mobile coronary care units [1,3,4] have substantiated the fact that most early deaths from myocardial infarction are due to disturbances of rhythm rather than pump failure, Systems to monitor cardiac rhythm have been instituted in ambulances[5,6] but such systems do not provide continuous monitoring of the electrocardiogram The purpose of this report is to describe and document the usefulness and application of a continuous electrocardiographic telemetry system

Methods

The system used at present is shown in Fig 1 The ECG telemetry originates from wherever the patient is. The bipolar ECG signal is amplified modulated and transmitted by a 1 8 watt transmitter (Motorola HT 220) that weighs 21 ounces (Fig 2) This signal is received in the ambulance and automatically retransmitted via a mobile repeater This signal is received in the CCU demodulated and monitored on the conventional CCU equipment It is also recorded on an analog tape system for permanent storage The ambulance ECG transmitter has an effective power of 40 watts. The frequencies utilized for continuous ECG transmission are exclusive and not shared by other agencies, thus insuring freedom from interruption

The voice communications are maintained on Hospital Emergency Administrative Radio (Motorola HEAR) Remote to the ambulance the technician utilizes a 5 watt transmitter (Motorola HT 220) and the signal is received in both

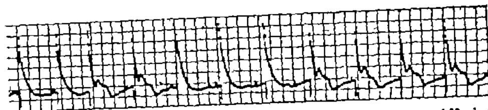
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3 Electrocardiogram transmitted from Case 1. Malfunction of the pacemaker was documented 30 minutes to admission of the patient to the hospital. Small P-QRS complexes are seen in the middle of the rhythm. The pacemaker fails to sense these complexes.

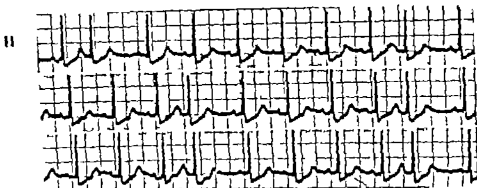


Fig. 4 Continuous rhythm strip transmitted from Case 2. (See text.)

warning.[7] Thus, it is theoretically sound to extend the concepts of CCU monitoring to prehospitalization monitoring. It is necessary, however, to obtain an exclusive frequency for continuous telemetry.

Several earlier reports[4] describing ECG ambulance telemetry have dealt only with intermittent ECG transmission. This limitation of ECG transmission is based on two factors. First, a single-channel system by necessity must utilize a given frequency for both voice communications and ECG telemetry. This is an elective limitation, however, and may be overcome simply by providing an additional channel. The need for continuous ECG monitoring during the early phase of the illness is amply illustrated by the high mortality during the first one or two hours after the onset of symptoms.

The communication system described in this report offers additional benefits. Experience with the mobile CCU has shown that false alarms and cancelled calls waste the time of trained personnel. Continuous telemetry and voice communications save time for the physician and nurse. This system places the physician at the patient's bedside by remote conversation rather than in person. Furthermore, the information obtained may permit circumvention of established Emergency Room delays.

One other advantage of this system is that it relieves the ambulance personnel of decision-making responsibility. The electrocardiographic diagnosis and medical instructions originate with the physician. Judgment and decision making rests upon the monitoring personnel in matters of the application of such measures as defibrillation and administration of an intravenous medication. Because such responsibility requires additional training, both theoretical and practical, the necessary educational support must be provided with the institution of the system.

Summary

A continuous electrocardiographic telemetry system is described which permits simultaneous voice communications. The

Table I

	Cases	*Normal sinus rhythm*	*Sinus tachycardia*	*Atrial premature beats*	*Paroxysmal atrial tachycardia*	*Sinus bradycardia*	*A V block*	*Premature ventricular contractions*	*Pacemaker*	*Ventricular tachycardia*	*Asystole*	*Undiffied*	*Ve tachy-*
Cardiac	31	5	12	3	2		1	5	1	1	2	2	1
Trauma	1	4	8										
Miscellaneous	26	9	10	1	1	1	1	2				3	3
Shock"	4	1	1			1		1					1

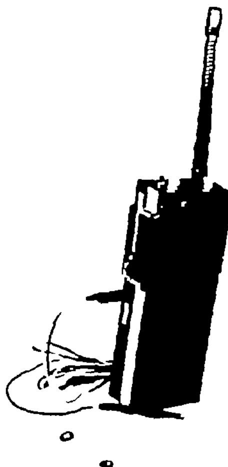


Fig 2 The hand-carried 1 watt transmitter and bipolar leads are shown. The weight of this unit is 21 ounces, and operates at a range in excess of 1 mile from the ambulance. Its range with mobile repeater is in excess of 30 miles.

QRS synchronized type is malfunctioning and fails to recognize the QRS complexes which are of very low amplitude. The patient was admitted to University Hospital, where rhythm strips recorded at the time of admission again showed a normally functioning pacemaker However pacemaker malfunction was repeatedly recorded while he was hospitalized

Case 2 The patient an 82 year-old woman, was discharged from the hospital in September 1970, with a diagnosis of acute myocardial infarction. In December 1970 she developed an abrupt onset of severe chest pain, localized primarily to the right side Because she had severe dyspnea, an ambulance was called by her daughter When the ambulance arrived ECG telemetry was instituted from the patient's bedside, and atrial premature beats were observed (Fig 4) Her family physician was notified of the history obtained and the arrhythmia, and direct admission to the CCU was arranged. Acute pulmonary embolism and coronary insufficiency were the final diagnosis.

Discussion

The system described in this report represents one approach to prehospitalization care It effectively provides continuous ECG monitoring by means of telemetry and simultaneous voice communications. This system has certain features which make it easily applicable These include (1) simplicity of operation (2) lightweight portable equipment, (3) continuous monitoring function of the electrocardiogram (4) continuous voice communication between hospital and ambulance personnel (5) extended range (30 miles) and (6) exclusive frequency for ECG transmission

Several investigators[6-8] have employed intermittent ECG transmission for detection of early arrhythmias in myocardial infarction However intermittent monitoring raises the possibility of missing a serious paroxysmal disturbance of rhythm since coronary care unit (CCU) and mobile CCU experience have brought attention to the fact that disturbances of rhythm may be transient. Furthermore asystole or ventricular fibrillation may appear with little fore-

Atrioventricular interaction in isorhythmic dissociation

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It has been observed that during atrioventricular (A-V) dissociation the independence between atria and ventricles may not be as complete as the term implies.[1-4] Thinking in this area has been stimulated by the fascinating work of Segers[5] demonstrating that pacemakers in juxtaposed frog hearts, or in myocardial fragments, tend to synchronize.

Numerous theories have been proposed to explain the interaction between atria and ventricles in man during complete and incomplete A-V block,[1-6] isorhythmic A-V dissociation,[7] and ventriculophasic sinus arrhythmia.[11] For the most part these theories have considered mechanical and reflex mechanisms and the electrotonic effect of ventricular depolarization. The relationship of pulse in the sinus node artery to sinus rate[8] and the analogy of cardiac pacemakers to coupled relaxation oscillators[4, 1] have also been considered.

Recently Levy and Zieske,[12] using an analogue computer, studied isorhythmic dissociation in dogs with complete heart block. They concluded that the interrelationship of P-R interval, arterial pressure, and sinus rate represents a "typical biological control system" that was the basis for A-V synchronization observed in their study.

The independent work reported in this paper confirms that of Levy and Zieske.[12] We chose, however, to study the interaction of atria and ventricles during acceleration of a subsidiary pacemaker in dogs with intact A-V conduction systems. Electrocardiographic (ECG) analysis, as in the present study, provides valuable information not apparent from computer patterns.

Methods

Experiments were performed on 26 mongrel dogs weighing 9 to 26 kilograms, anesthetized with alpha-chloralose, 100 mg. per kilogram intravenously. Additional doses of anesthetic were given as needed. The trachea was cannulated and the animal mechanically ventilated with room air. The heart was exposed via a right lateral thoracotomy incision and pericardiotomy. Bipolar plunge wire electrodes were inserted into the regions of the sinus node (SN) and Bachmann's bundle (BB) in all animals for the purpose of recording by

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data observed suggest that continuous ECG telemetry is a useful tool in the prehospitalization detection of arrhythmias in patients with coronary heart disease The instituting of earlier therapy for arrhythmias may reduce the incidence of early death

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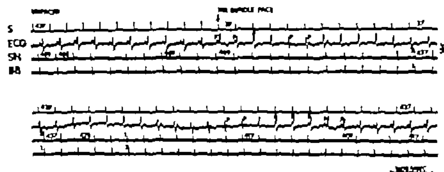


Fig. 1. Sinus acceleration during His bundle pacing following an 8 second period of retrograde sinus capture. S = stimulus during the control period (unpaced) and during His bundle pacing (onset indicated by arrow).

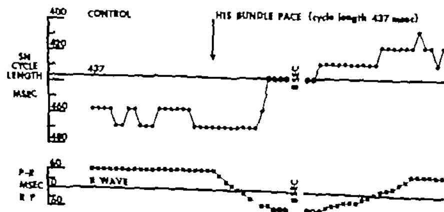


Fig. 2. The changes in *SN* cycle length (above) and *P-R* and *R-P* intervals (below) during His bundle pacing are plotted for the record in Fig. 1. Open circles correspond to the period of retrograde sinus capture.

strip of this figure. The entire sequence then repeats, and continues to do so as long as His bundle pacing is maintained. This figure illustrates that when the P-R interval is altered during pacing slightly in excess of the spontaneous rate, the sinus node accelerates *despite* initial retrograde capture.

The record in Fig. 1 is displayed graphically in Fig. 2. Sinus node cycle length is plotted in the upper panel, and the corresponding P-R and R-P intervals in the lower panel. These intervals are plotted as distances above and below the R wave and serve as a visual aid to indicate the changing P-R relationship during pacing. Following the initiation of His bundle pacing, at a cycle length of 437 msec., retrograde sinus capture occurs (open circles) after a brief period of A-V dissociation. A further decrease in sinus cycle length is then recorded as the sinus accelerates and escapes from retrograde capture. The altered P-R relationship preceding and during sinus acceleration induced by His bundle pacing is indicated below. At faster rates of pacing sinus acceleration was not seen and a sustained His rhythm with 1:1 retrograde sinus capture occurred. At slower rates of pacing (but in excess of the spontaneous rate) alternating periods of synchronization during A-V dissociation and sinus rhythm were seen in the absence of retrograde sinus capture. The specific pattern seen was, therefore, rate dependent in all animals in this group.

Atrial fusion beats were invariably recorded when sinus and pacing rates were not too dissimilar and are illustrated in selected portions of a continuous record in Fig. 3. In panel *A* multiple atrial electrogram recordings define the antegrade sequence for atrial depolarization during sinus rhythm (*1 to 6*). The sinus cycle length varies between 340 and 344 msec.

means of a technique previously described.[13] In four animals additional electrograms were simultaneously recorded from the right atrial appendage (RAA), left atrial appendage (LAA), posterior left atrium (LAP), and the proximal portion of the coronary sinus (CS). A standard Lead II ECG was recorded in all animals. Bipolar plunge wire electrodes were inserted into the mid right ventricle (20 dogs) and the His bundle (9 dogs)[14] for the purpose of pacing. His bundle pacing was validated when the interval from the His bundle deflection to the onset of ventricular activation (VA) during the control period was the same as the stimulus to VA interval during pacing and when the QRS morphology during the control and pacing periods was similar.

The heart was paced slightly in excess of threshold with 1 msec. square wave pulses using Textronix waveform and pulse generators and a Bioelectric stimulus isolation unit. The pacing rate was set to exceed the spontaneous rate and was initiated within the P-R interval corresponding to the pattern seen clinically when acceleration of moderate degree occurs in a subsidiary pacemaker of the heart.

A metal cannula was inserted into the right atrium via an external jugular vein and a rigid polyethylene catheter was passed into the descending aorta via a femoral artery. Right atrial (RAP) and aortic pressures (AP) were recorded with the use of Statham P23Db pressure transducers in 17 dogs. Change in aortic blood flow in units of deflection was measured in the proximal aorta by means of an electromagnetic flowmeter (Medicon Multiflo) in 11 dogs. All recordings were made on an Electronics for Medicine multichannel oscillographic recorder at paper speeds of 50 to 100 mm. per second.

Excision of the right and left stellate ganglia and upper thoracic sympathetic chain (BSTG) was performed in 10 dogs via a right and left lateral thoracotomy in the third intercostal space. The functional completeness of sympathectomy was confirmed by the absence of a change in heart rate (±3 beats per minute) following bilateral common carotid occlusion low in the neck.[15] Bilateral cervical vagotomy was performed in 10 dogs by transection of the right and left vagosympathetic trunks. Both BSTG and vagotomy were performed in the same dog in 7 instances. By this extrinsic denervation technique we attempted to separate sympathetic and parasympathetic outflow to the heart from the central nervous system.

Results

ECG patterns during His bundle and ventricular pacing

GROUP A. ANIMALS WITH RETROGRADE CONDUCTION PRESENT. In this group the atrial response during His bundle (6 dogs) and ventricular (10 dogs) pacing was similar. In all dogs sinus acceleration occurred after an initial period of retrograde sinus capture as depicted in Fig. 1. In this record the stimulus (S) is monitored during the control (unpaced) portion of the record to indicate visually the relative rate of stimulus to atrium. The SN and BB electrograms are recorded to distinguish antegrade from retrograde conduction since SN precedes BB during sinus rhythm with the order reversed during retrograde sinus capture. During the control (unpaced) portion of the record sinus cycle length varies between 458 and 469 msec. and SN precedes BB. With the onset of His bundle pacing A-V dissociation occurs, since ventricular rate exceeds sinus rate. After 12 beats the sinus node is captured in retrograde fashion as indicated by BB preceding SN and sinus rate and ventricular rate become identical. As a consequence of the altered P-R interval accelerating forces develop. After 8 seconds, the sinus accelerates* and escapes from retrograde capture (lower strip), sinus cycle length decreases, SN precedes BB and an upright P wave appears after the QRS. A-V dissociation continues as the sinus cycle length decreases progressively. When the accelerating forces shorten the sinus cycle length sufficiently SN becomes the pacemaker for the heart and the stimuli fall within the refractory period of the His bundle (right-hand portion, lower strip). Not shown is the subsequent slowing of sinus rate followed by the restoration of effective His bundle pacing as in the top

*Sinus acceleration specifically refers t[illegible] increase in sinus rate (shorter sinus cycle length) [illegible] compared t[illegible] the control portion of the record.

preceding cycles, capture is prevented because of concealed retrograde conduction. This is indicated by an increased P R interval during capture with a normal P R interval thereafter At slightly slower pacing rates (but in excess of the spontaneous rate) the P wave appeared alternately to the right and left of the QRS. Under these conditions of pacing the magnitude of the accelerating forces was sufficient to maintain a short R P interval and thereby prevent ventricular capture.

Hemodynamic changes during ventricular and His bundle pacing Changes in pressure and flow were similar for His bundle and ventricular pacing and occurred in all animals. A representative recording during ventricular pacing (from an animal in Group A) is shown in Fig 5 The large and small dots at the top of the record correspond to the stimulus and sinus node respectively and serve as a visual aid to changes in sinus rate with respect to ventricular rate. During the control (unpaced) period recorded in the panel on the left, it can be seen by inspection that the stimulus rate exceeds sinus rate but that during right ventricular pacing sinus rate and pacing rate become nearly equal and correspond to the 'clustering' of the P wave around the QRS. Initially during pacing AF and AP are reduced and RAP increased when compared to the control record. During this period the atrium is contracting against a closed A V valve and visibly distends. Some degree of tricuspid regurgitation probably also contributes to the atrial pressure rise in some experiments. The fall in AP and AF during this period follows the loss of the atrial contribution to ventricular filling As a consequence of these hemodynamic changes, accelerating forces develop which increase the sinus rate. Sinus acceleration restores the A V activation sequence toward normal. Pressures and flow return to control levels. The accelerating forces then decrease, the sinus slows, the P wave moves back into the QRS and the cycle repeats. The above hemodynamic changes varied in predictable fashion according to the particular ECG pattern described previously for animals in Groups A and B

Per cent sinus acceleration during His bundle and ventricular pacing before denervation Sinus acceleration was calculated from the ratio of the shortest SN cycle length during maximum acceleration to that recorded during the control period The results from Groups A and B were pooled. During His bundle pacing the average sinus acceleration was 7 6 ± 1 0 per cent (mean ± S.E. P < 0 001) with a range of 4 to 13 per cent. Sinus acceleration during ventricular pacing averaged 9 6 ± 0 9 per cent (P < 0 001) and did not differ significantly (P > 0 10)† from that observed during His bundle pacing

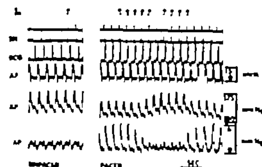


Fig. 5 Corresponding changes in right atrial (*RAP*) and aortic (*AP*) pressures and aortic flow (*AF*) during isorhythmic dissociation induced by ventricular pacing. See text.

Effects of denervation on induced sinus acceleration. The results of denervation are summarized in Table I Bilateral stellatectomy and thoracic ganglionectomy (BSTG) alone or combined with bilateral vagotomy greatly attenuated or abolished the response to pacing (P < 0 005) Bilateral vagotomy alone did not significantly alter the response (P > 0.1)

It was noted consistently that after BSTG when cardiac sympathetic tone was withdrawn, the rise in right atrial pressure with pacing was minimal when compared to that seen before stellatectomy In an attempt to restore the rise in RAP to the degree seen before denervation 6 per cent dextran (100 to 150 c.c.) was infused In the four denervated‡ animals studied by this technique, sinus acceleration before dextran was 0 per cent in three and less

*Calculated by the standard t test for paired variables.
†Calculated by the standard t test for unpaired variables (ventricular and His bundle pacing were not always done in the same animal)
‡Combined BSTG and vagotomy

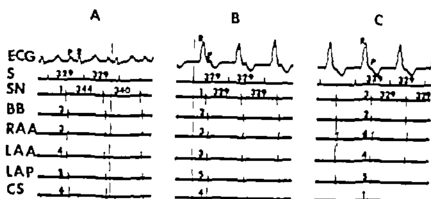


Fig. 3 Selected portions of a continuous record demonstrating sinus rhythm (panel *A*) synchronization, and atrial fusion during isorhythmic dissociation induced by ventricular pacing (panel *B*) and retrograde sinus capture (panel *C*). The numbers *1* through *6* indicate the order of atrial activation.

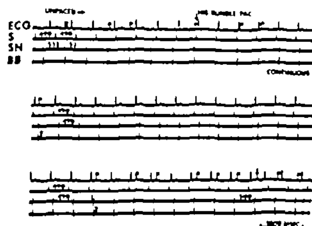


Fig. 4 Synchronization (strips *2* and *3*) during isorhythmic dissociation induced by His bundle pacing in excess of spontaneous rate. The record is continuous. The open arrow in the bottom strip indicates the return to sinus rhythm as the sinus rate decreases slightly (cycle length 500 msec.) allowing for ventricular capture. Abbreviations as before.

During ventricular pacing (panel *B*)* the sinus rate has increased and equals pacing rate. The normal SN BB and right atrial appendage (RAA) sequence indicates a dissociation between sinus and ventricular pacemakers. However the left atrial appendage (*LAA*) posterior left atrium (LAP) and coronary sinus (CS) sequence indicates retrograde capture of a *portion* of the atria. Hence the upright P waves in Lead II which follow the QRS at a fixed interval represent atrial fusion beats. The pattern seen in panel *B* is maintained for 30 beats, and is followed by retrograde sinus capture as shown in panel *C*. With a slightly slower rate of ventricular pacing retrograde sinus capture did not occur and the atrial activation sequence shown in panel *B* changed instead to that shown in panel *A*. Since the P wave in panel *C* appears upright (although less so than in panel *B*) this figure emphasizes that the standard ECG may not distinguish between synchronization of *two* independent pacemakers and retrograde capture of the atria from *one* pacemaker.

GROUP B ANIMALS WITH RETROGRADE CONDUCTION ABSENT. In this group bundle of His (3 dogs) and ventricular pacing (10 dogs) gave similar results. The ECG patterns observed were rate dependent as in Group A but were modified by the absence of retrograde conduction in this group. Sinus acceleration with synchronization of independent pacemakers was observed during pacing in all animals. Fig. 4 illustrates a continuous record from a representative experiment. SN cycle length during the control (unpaced) period varies between 521 and 532 msec. During His bundle pacing with a stimulus cycle length of 490 msec. SN accelerates (middle strip) and the P wave appears to the right of the QRS complexes as an upright deflection with a cycle length similarly of 490 msec. Since SN precedes BB as during the control period the atria and ventricles are depolarized independently but now beat at the same rate. This relationship of atrium to ventricle is maintained for the next 23 beats at which time the sinus rate *decreases slightly allowing for ventricular capture* by the sinus pacemaker and restoring sinus rhythm (open arrow). In the

*The long interval from stimulus to QRS indicates an intramyocardial (or epicardial) position of the pacing electrodes.

the dissociation is complete or incomplete[17] does not significantly alter this pattern.

Levy and Zieske[12] suggest that during synchronization in isorhythmic dissociation the changes in arterial pressure are translated into rate changes by the classical baroreceptor reflex[18, 19] primarily and by changes in the caliber of the sinus node artery[6] to a lesser extent. While these considerations adequately explain the results of the present study we suggest that right atrial stretch may be an additional factor. The basis for this speculation is as follows. Blinks[20] noted a positive chronotropic effect of increasing right atrial pressure in the intact isolated dog heart and the isolated rabbit right atrium and suggested mechanical tension as its basis. From the results of similar experiments on several mammalian species, Pathak[21] concluded that the pressure acceleration response is a general phenomenon. Lange and coworkers[22] recorded an increased rate of discharge from cells in the isolated cat sinoatrial node during stretch and Brooks and associates[23] noted cardioacceleration in the dog during localized stretch of the in situ sinoatrial region. In the present study we observed that atrial pressure changes always preceded sinus rate changes and occurred simultaneously with changes in arterial pressure. The simultaneous partial restoration of atrial pressure and sinus rate changes with dextran following total extrinsic cardiac denervation suggests that right atrial stretch may have played a role in these experiments. Furthermore, preliminary experiments involving paired ventricular pacing and right atrial venting would appear to validate this speculation.

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Table I. Per cent sinus acceleration during ventricular pacing before and after denervation

Procedure	No. of dogs	Mean	± S.D.	± S.E.M.	t	P*
BSTG + bilateral vagotomy						
Before	7	10.9	4.5	1.7		
After	7	0.7	1.1	0.4		
Difference between observations		10.2	5.1	1.9	5.2	<0.005
BSTG						
Before	8	11.0	3.9	1.4		
After	8	0.6	1.4	0.5		
Difference between observation		10.4	4.2	1.5	7.0	<0.001
Bilateral vagotomy						
Before	7	11.1	4.1	1.5		
After	7	6.7	4.2	1.6		
Difference between observations		4.4	6.2	2.3	1.9	>0.05†

*P values are calculated by the standard t test for paired variables.
†Not significant.

than 1 per cent in one and increased to 4 or 5 per cent after dextran as the rise in RAP was restored toward normal. Since sinus acceleration in these animals before denervation ranged from 8 to 14 per cent the response to pacing was attenuated despite dextran infusion.

Discussion

The interrelationship of P-R interval, arterial pressure, and sinus rate recently reported by Levy and Zieske[13] was similarly observed in the present study in dogs with A-V conduction intact. Under the conditions of this study synchronization during isorhythmic dissociation was also noted; however, the specific ECG pattern was determined by several factors. These factors included (1) the presence or absence of retrograde conduction, (2) the relative rates of atrium and ventricle, (3) the magnitude of the accelerating forces, and (4) the responsiveness of the sinus node.

On the basis of this and other studies we believe that the current concept of isorhythmic dissociation as a chance phenomenon[14] should be modified and should recognize the dynamic interaction between atria and ventricles that may occur in this arrhythmia. Furthermore, the present study extends the observations by Waldo and associates[8] regarding the morphology of the P wave during isorhythmic dissociation. The authors present evidence in man that the upright P wave in the inferior leads recorded during synchronization represents in fact not two but one cardiac pacemaker discharging with retrograde atrial capture. We have demonstrated, however, that synchronization* of primary and subsidiary pacemakers may occur during isorhythmic dissociation and be associated with a P wave upright in the inferior leads, seemingly linked to and following the QRS (Fig. 3).† In addition this phenomenon may also be seen when two pacemakers synchronize during retrograde conduction that penetrates into only a portion of the atrium and results in atrial fusion complexes (Fig. 4, panel *B*).

For the reasons stated above it should be evident that the standard ECG frequently does not permit one to distinguish A-V dissociation with synchronization of two pacemakers from the situation in which one pacemaker captures the atria in retrograde fashion and controls the entire heart. We prefer, therefore, to consider isorhythmic dissociation an electrocardiographic *pattern*, the salient features of which are (1) the similarity in atrial and ventricular rates and (2) P waves which at times may precede or follow the QRS but remain in close proximity to it. Whether

*Two interacting pacemakers discharging at equal or nearly equal rates.
†The ECG pattern depicted in this figure is of special interest because of its remarkable similarity to the record from 14-year-old girl with myocarditis reported by Schubart and associates[3] in their Fig. 1.

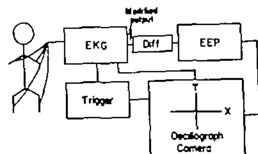


Fig. 1. Electronic arrangement. Unmodified ECG voltage V is fed to Y axis. Derivative dV/dt is amplified in the higher frequency response EEP (electrocardiograph, electroencephalograph, phono) channel and fed to X axis.

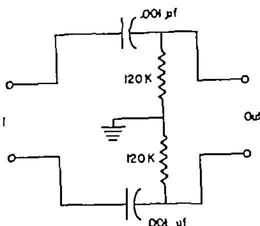


Fig. 2. RC differentiator. Values chosen to record 20 H events with less than 1 per cent error.

tion of specific mechanisms underlying the recorded patterns.

Methods

A standard twelve-lead electrocardiogram and phase plane loops of V_1 and V_6 were displayed and photographed on an Electronics for Medicine oscillographic recorder, the latter by placing voltage (V) on the vertical axis and the first derivative of voltage (dV/dt) on the horizontal axis (Fig. 1). The first derivative (dV/dt) was obtained with a simple RC differentiator (Fig. 2). The time constant of this differentiator is 0.12 msec. giving a phase angle of 89.2 degrees for 20 Hz. This is within 0.8 per cent of the correct angle of 90 degrees for a sine wave derivative. It should be mentioned that, in order to obtain minimal phase shift error, the electrocardiograph, electroencephalograph, phono (EEP) amplifier was set at an upper cutoff frequency of 200 Hz. Although 60-cycle and movement artifacts are not inherently rejected in the differentiating circuit, interference from these factors was not of significant concern in the interpretation of phase plane cardiograms, as will be discussed later.

The limiting factor in determining the fastest phenomena for which a phase plane cardiogram can be recorded with this system is the timing dots of the oscillographic recorder. The dot adjustment was set for 0.002 sec. timing or 500 per second. If we assume that at least 3 dots are required to define any deflection, the maximum frequency that can be observed is 166 Hz.

The output of the ECG amplifier was modified to obtain more drive for the differentiator (Fig. 3) and therefore required less amplification of the derivative, thus minimizing noise introduced by amplification.

A sine wave generator was used to calibrate the system. With the frequency set at 20 Hz and maximum voltage (V_{max}) at 0.5 mv, the following relationships were used to calibrate dV/dt:

$$V(t) = V_{max} \sin \omega t$$

$$dV/dt = V_{max}\,\omega \cos \omega t$$

$$dV/dt = 0.5 \times 125.6 \cos \omega t = 62.8 \cos \omega t$$

where

$V(t)$ = voltage at any time

V_{max} = ½ peak-to-peak sin wave amplitude

ω = 2πf angular frequency in radians per second

$V_{max}\,\omega = (dV/dt)_{max}$

With V_{max} (0.5 mv) set for a 5 cm deflection on the Y axis, and $(dV/dt)_{max}$ (62.8 mv per second) set for a 5 cm. deflection on the axis, a 10 cm. diameter circle is displayed. The 20 Hz sine wave was chosen since its rise time of 0.025 sec. approximates the rise time of the R wave.

Triangular waves and sine waves were viewed to assess the ability of the method to reveal minor changes in wave contour.

Fig. 4 shows the comparison between a perfect (lower trace) and an imperfect (upper trace) sine function. Inspection of the two sine wave patterns does not reveal

A new approach to clinical electrocardiography
The phase plane cardiogram

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Since the late nineteenth century, the electrocardiogram as a display of voltage plotted against time has provided an invaluable tool in the study of electrical activity in the normal and diseased heart. Understandably, the simplicity and reliability of the basic technique as a diagnostic tool have to the present time all but precluded serious innovation or modification.

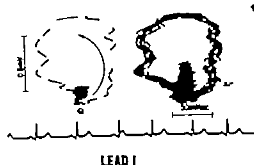
In 1938 Wilson and Johnston described the vectorcardiogram, a two-dimensional plot of cardiac electromotive forces in a single plane.[1] Although the vectorcardiographic tracing inherently contains no more information than is present in ordinary scalar recordings, the coordinated vectorial display of voltage emphasizes relationships not readily apparent in the scalar tracing.

In a similar sense we have become interested in exploring the possible value of another approach—phase plane trajectory—toward *enhancing the analytical efficacy* of electrocardiographic data. We believe that this maneuver, which portrays voltage (V) of a given lead coordinated against its first time derivative (dV/dt), offers exquisite sensitivity for close inspection of the QRS complex throughout its time course. *It is hoped that the information so recorded will allow for more rigorous analysis of ventricular activation in normal and disease states.*

Phase plane trajectories consisting of an X-Y display of voltage against the time derivative have been employed by a number of investigators in studying the cell membrane characteristics of a variety of electrically active tissues.[2-4] When applied to single cell preparations where information in regard to system constants can be secured, the method may reveal specific knowledge as to membrane potentials and ionic conductances. For a more rigorous discussion of these applications, the reader is referred to the original paper by Jenerick.[3]

It must be emphasized that our application of the phase plane here is designed to take *advantage of the inherent sensitivity* of the method to minor aberrations in wave form of the QRS complex, and is not intended at this time to be utilized in delinea

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LEAD I

Fig. 7 Standard ECG and phase plane cardiograms of Lead I. *Upper left.* Single loop. *Upper right.* Crude average obtained by superimposition of several loops. Correlation points to QRS complex are designated in counterclockwise rotation.

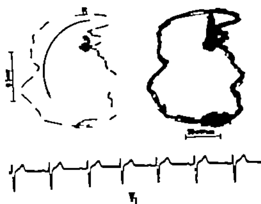


Fig. 8 Standard ECG and phase plane cardiograms of Lead V. *Upper left.* Single loop. *Upper right.* Crude average obtained by superimposition of several loops. Correlation points to QRS complex are designated in counterclockwise rotation.

voltage and zero dV/dt, the wave proceeds along constant dV/dt line *A* until the positive amplitude *a'* is reached. At amplitude *a* the loop swings over to a constant negative dV/dt line *B* through zero point *b*. With voltage now going negative dV/dt continues constant along *C* to negative amplitude *c'* where dV/dt once again swings positive and proceeds along a constant line *D* to finish at zero point *d'*.

Finally data were obtained from 9 normal volunteers and 5 patients with left ventricular hypertrophy. In most instances several consecutive phase plane loops were superimposed to provide a crude average of recorded events.

Results

A typical normal Lead I tracing is presented in Fig. 7. The analytical advantage of phase plane recording is demonstrated by examining the contour of QRS in the scalar display in relation to the loops shown. It would be reasonable to suggest from the standard ECG that the QRS complex closely resembles a triangular wave and that no confident conclusions could be drawn concerning minor aberrations in contour. However examination of the phase plane cardiogram reveals that considerable detailed information is actually present and is accentuated by this mode of visualization. If indeed the true wave shape had been simply triangular then as shown in Fig. 5 the phase plane should have produced a rectangular display with smooth borders.

If one considers the loop in counterclockwise rotation, the initial downward deflection begins the Q wave. The trace then jumps onto a vertical straight-line excursion containing numerous notches until the peak of R is reached. If one neglects for the moment the small inflections, this region of the loop might support the idea that the initial phase Q R in scalar Lead I rises linearly with time since the loop shows that Q proceeds to R via a constant dV/dt line. However as R falls to the baseline significant nonlinearities are seen, suggesting that in this example potentially meaningful diagnostic parameters may reside in this downslope. Reinforcing this idea is the fact that normal phase plane cardiograms for given leads appeared to be quite similar among the individuals tested showing repeatable notching patterns. It might be noted here that P and T waves appear only in the initial dense region of the loop as a cluster of small-amplitude phase plane patterns and in no way obscure interpretation of the ventricular complex.

Fig. 8 portrays recordings obtained from Lead V_1. Comparing loops to the scalar trace once again reveals that substantial deviations in wave shape are uncovered in the phase plane which are not confidently seen in the standard ECG. Of special interest here is the sub loop appearing at S. The fact that dV/dt inscribes this pattern going through zero on the V axis predicts a "notched" QRS complex on the scalar recording. Although an aberration appears on the ECG both its qualitative and quan-

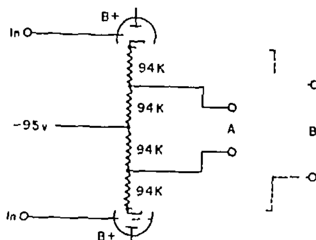


Fig 3 Electronic modification of standard E for M (Electronics for Medicine) ECG amplifier *A* represents normal output configuration fed to Y axis. *B* represents takeoff point for differentiator Higher signal level at *B* reduces system noise presented to Y axis.

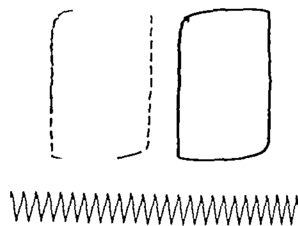


Fig 5 Scalar and phase plane portrayal of triangular function. *Left* Single loop. *Right* Superimposed loops.

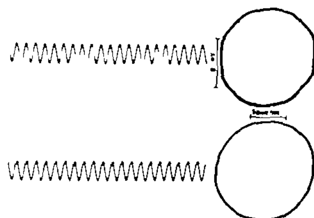


Fig 4 Scalar and phase plane portrayals of calibration sine function. *Upper* Generator produces sine wave with minor flaw not visible to eye but seen in loop as octagon-like pattern. *Lower* Generator producing more perfect sine function displays a more circular loop.

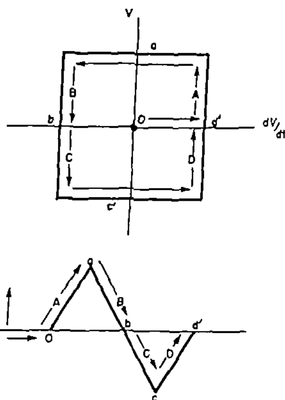


Fig 6 Comparison of idealized scalar triangular wave (voltage plotted against time, *lower figure*) with its corresponding phase plane display (*upper figure*)

even a slight difference between the rising phase and the falling phase However the fault is clearly revealed in the phase plane patterns by the octagon like appearance of the upper loop The vertical straight line portions represent a period of constant dV/dt as would be the case if some fraction of the wave were changing linearly rather than sinusoidally *This point is emphasized in Fig 5* where the linear regions of the *triangular* wave are portrayed as vertical lines in the phase plane, yielding a rectangular display for the function

Fig 5 also compares the single loop (left hand pattern) with the superimposed recording (right hand pattern) The fact that a single loop is quite reliable and repeatable *is evidenced by the similarity* between the two as is also the case with recordings in patients.

The explicit relationship between the triangular wave and its phase plane trajec*tory is perhaps more easily visualized in* the idealized comparisons presented in Fig 6 From the origin *(O)* representing zero

is less significant. If this observation proves to be valid in experiments on a larger scale, then perhaps the diagnostic efficacy of any given ECG lead may be greatly enhanced. At any rate, we tentatively suggest from the findings that, with this singularly simplistic analysis of phase plane cardiograms, new parameters for electrocardiographic analysis are made available. The reader might be reminded that arbitrary parameters were chosen for quantitation in this preliminary work and it is possible that other methods of measuring loop coordinates could prove to be more significant.

The existence of considerable notching in the phase plane loops from certain patients was mentioned earlier. The extent to which the notching may be correlated with subtle changes in ventricular activation is currently being investigated in both animals and human beings.

Perhaps the greatest importance of the findings reported here lies in the fact that there is a considerable amount of information contained within the QRS complex, not easily detected by means of classic scalar electrocardiographic methods, and that this information is readily accessible and quantitatable through phase plane analysis. In addition, it should be emphasized that the loops described are easily recorded on commonly available oscillographic devices without significant alteration.

The relationship between the phase plane data presented in this paper in terms of diagnostic capability can only be determined by future large-scale applications of the technique.

Summary

A method for increasing the diagnostic capability of clinical electrocardiography is presented. The coordinated display of voltage against the time derivative of voltage, i.e., phase plane cardiogram, was found to be remarkably sensitive to subtle aberrations in QRS contours not easily visualized in the standard electrocardiographic portrayal—voltage against time. In preliminary studies, the method revealed statistically significant differences in selected phase plane parameters of patients with left ventricular hypertrophy as compared to normal subjects. The method allows information gained by means of standard clinical procedures to be viewed in a fashion which reveals details otherwise lost. The extent to which this new knowledge concerning the ECG can be related to or be predictive of disease states can only be assessed by future intensive application of the technique.

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*Table I**

		Normal		LVH
Lead V_1	V	1.1 ± 0.2	0.05 > P	2.0 ± 0.2
	dV/dt	106 ± 16	0.1 > P > 0.05	146 ± 25
	$\frac{dV/dt}{V}$	103 ± 15	0.05 > P	72 ± 6
Lead V_6	V	1.3 ± 0.1	0.1 > P > 0.05	2.0 ± 0.5
	dV/dt	90 ± 9	0.2 > P > 0.1	121 ± 29
	$\frac{dV/dt}{V}$	72 ± 6	0.2 > P > 0.1	61 ± 8

*Means and standard errors are tabulated. Values were determined from maximum phase plane coordinates from Leads V_1 and V_6 using 9 normal subjects and 6 patients with left ventricular hypertrophy. P values were calculated using Student t test for small samples.

titative natures are far better ascertained in the loop.

Mentioned earlier was the problem of 60-cycle and movement artifact interference. The contribution of 60-cycle may be revealed by examining the characteristics of the loop at its origin. Here a dot artifact may be visualized as a small oval shaped portion of the pattern appearing among the cluster of P and T wave components. This represents 60-cycle and noise recorded during the isoelectric interval. It can be seen that the maximum magnitudes projected from the center of the oval constitute a very small fraction of the over-all loop excursions. This fact is emphasized in the superimposed tracing where the thickness of the loop perimeter would indicate the contribution of random events such as 60-cycle and movement artifacts. It appears then that, when normal precautions to reduce electrical and mechanical interference are taken, even relatively subtle aspects of the loops can be faithfully reproduced.

Table I compares phase plane parameters taken from Leads V_1 and V_6 using normal subjects and patients with left ventricular hypertrophy. In this study an extremely simple approach toward quantitating the loops was employed, i.e., the maximum V axis and dV/dt axis excursions were measured as perpendicular to the appropriate zero lines. These magnitudes and their ratio are tabulated.

Discussion

At this point it seems evident that new and possibly useful information is offered by the technique described. The most obvious problem is the manner in which the findings might be correlated with or be predictive of disease states. In this respect this paper does not attempt to do much more than offer the idea and perhaps suggest one of probably dozens of methods by which the data might be analyzed.

From well-established ECG findings, one might predict that the voltage amplitude (V) would be altered in left ventricular hypertrophy (LVH). That this is the case is seen from the significant differences in V between normal subjects and patients in both Leads V_1 and V_6 (Table I). Of added interest is the dV/dt value which appears to indicate significant differences, although the limited number of patients examined must qualify the reliability of the probabilities shown. As stated, Lead V_1 yields a highly significant difference in the loop ratio $\frac{dV/dt}{V}$ whereas the same ratio in V_6

surgery or alternatively long term therapy with the aldosterone antagonist spironolactone[1, 11,14 19] is indicated in the patients with diffuse bilateral adrenal abnormalities.

A possible line of approach to a distinct diagnosis was suggested by the reports of Distler and associates,[21] Baer and co-workers,[20] Biglieri and colleagues,[22] and Ferriss and his confreres,[23] all of whom indicated that the biochemical abnormalities were generally more marked in the patients with tumors than in the group of patients who did not have tumors. Thus, the mean of the various aldosterone values, and the mean plasma (or serum) concentrations of sodium and bicarbonate were higher in tumorous patients, and the mean plasma concentrations of renin and potassium were lower in this group Despite these differences, which in the series of Ferriss and colleagues[23] achieved statistical significance for plasma aldosterone renin potassium, and bicarbonate concentrations (and in that of Baer and co-workers[20] for serum sodium potassium and bicarbonate concentrations and for aldosterone excretion) the ranges of results were wide and of different magnitudes in the two groups. For this reason straightforward interpretation of the biochemical data (e.g by linear discriminant analysis) did not permit a confident prediction of the nature of the adrenal lesion and it was therefore decided to apply the technique of circumscribing quadric analysis[24] to the problem the relevant calculations being performed by computer

Principles of quadric analysis

The basic ideas of quadric analysis may be explained simply in terms of a single test, i.e. as quadric analysis in one dimension. In Fig 1 the open circles represent the test results on patients with disease 1 the solid triangles the corresponding results on patients with disease 2. The mean results in the two groups are denoted by $\bar{x}_1$ and $\bar{x}_2$, and the associated standard deviations by s_1 and s_2. The two curves shown are then the fitted frequency curves for the two groups. The rationale underlying the construction of circumscribing quadrics in this context is then simple. In considering how typically an observation x conforms to a group we often assess its departure from conformity in terms of its standardized distance (i.e the number of standard deviations the observation is from the mean of the group) For an observation x the standardized distance relative to *group 1* will be $|x - \bar{x}_1|/s_1$ its standardized distance from the mean of group 2 will be $|x - \bar{x}_2|/s_2$. Equivalently (and in the extension to more than one dimension) we can use *the squares* as such measures

$$d\ (x) = \frac{(x - \quad)^2}{\ } \qquad d\ (x) = \frac{(x - \quad)^2}{s^2}$$

We can then construct our circumscribing "quadric by moving out equally in both (in general *all*) directions a (standardized) distance equal to that of the most extreme result of *the* group. The intervals so constructed (*AB* and *CD* in Fig 1) are then the circumscribing quadrics. If the *quadrics* for the two groups do not overlap then complete diagnostic separation has been achieved geometrically

In the example shown in Fig 1 however the quadrics do overlap and further calculations based on considerations of probabilities are necessary to classify a patient. Allocation to a disease group may then be based on the "likelihood ratio which is simply the probability that disease 1 would give rise to the observed test result divided by the probability that disease 2 would give rise to that result. *For* patient *P* in Fig 1 the estimated likelihood ratio is *RP/QP* which is less than unity indicating that disease 2 is the more probable For patient *P'* the estimated likelihood ratio is greater than unity giving an assignment to disease *1* in this case. Thus the

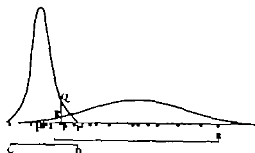


Fig. 1 Schematic diagram to illustrate principles of quadric" analysis in one dimension. Circles and triangles indicate patients with two different diseases. *AB* and *CD* are the respective quadrics.

Quadric analysis in the preoperative distinction between patients with and without adrenocortical tumors in hypertension with aldosterone excess and low plasma renin

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In 1955 Conn and others[1,2] described patients with hypertension, hypokalemia, and hyperaldosteronism due to the presence of benign adrenocortical adenomas. The abnormalities in such cases were usually found to be corrected by excision of the tumors.[2,3] The subsequent introduction of plasma renin measurement added further precision to diagnosis, since patients with adrenocortical adenomas have low or subnormal plasma renin levels in contrast to the elevated plasma renin in hypertensive patients with hyperaldosteronism associated with a renal or renal artery lesion or the malignant phase.[4-9]

More recently, however, it has become clear that the situation is less simple, since all of the principal features regarded as typical of an aldosterone-secreting adrenocortical adenoma (hypertension, hyperaldosteronism, hypokalemia with excessive urinary potassium loss, and low plasma renin) have been observed in the absence of an adrenocortical tumor.[10-14] In the latter instances, the adrenal cortices have been found to have hyperplasia of the zona glomerulosa, frequently with nodular changes, or even a normal histological appearance.

If preoperative differentiation between the two main groups of cases with hyperaldosteronism and low plasma renin could be achieved, this would be of considerable clinical value, because while unilateral adrenalectomy[2,3] or even localized excision of the tumor[5] may be effective in patients with an adenoma, more extensive bilateral

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Table I. Detailed results of analyses performed in the five series of patients

Source of data	Pathology	Tests available*	External analysis			Internal analysis		
			Tests used	Properties served		Tests used	Properties served	
				Geometry	Likelihood-ratio		Geometry	Likelihood-ratio
Ferriss, 1970	Adenoma 20	1-8	—	—	—	1-8	20/20	20/20
	Non-tumorous 11	1-8	—	—	—	1-8	0/11	11/11
Further cases added to above series since 1970	Adenoma 7	1-8	1-8	2/7	7/7	—	—	—
	Non-tumorous 1	1-4, 7 8	1-4, 7 8	0/1	1/1	—	—	—
Distler, 1969	Adenoma 5	1-3, 5-8	1-3, 7 8	5/5	—	I) 2, 3, 5, 6	5/5	—
						II) 2, 3, 7 8	5/5	—
						III) 2, 3, 4, 8	4/5	—
	Non-tumorous 5	1-3, 5-8	1-3, 7 8	1/5	2/5	I) 2, 3, 4, 6	4/5	—
						II) 2, 3, 7 8	5/5	—
						III) 2, 3, 6, 8	5/5	—
George,[12] 1970	Adenoma 13	1-4, 7-8	1-4, 7 8	3/13	13/13	1-4, 7 8	13/13	—
	Non-tumorous 6	1-4, 7-8	1-4, 7 8	0/6	0/6	1-4, 8	5/6	5/6
Baer 1970	Adenoma 12	1-4, 6-8	1-4, 7 8	3/12	12/12	1-4, 6-8	12/12	—
	Non-tumorous 11	1-4, 6-8	1-4, 7 8	0/11	0/11	1-4, 6-8	9/11	10/11
Ebury 1968	Adenoma 12	1-4, 7 8	1-4, 7 8	5/12	11/12	1-4, 7 8	12/12	—
	Non-tumorous 2	1-4, 7 8	1-4, 7 8	0/2	0/2	1-4, 7 8	2/2	—

*Diagnostic tests coded thus: age, serum (or plasma) sodium 3 serum potassium 4 = serum bicarbonate; 5 = plasma renin concentration, 6 aldosterone secretion, excretion, or plasma concentration; 7 = systolic B.P.; diastolic B.P.

a single benign adrenocortical adenoma was found in 20. No tumor was seen in eleven and the adrenal glands of nine of these showed hyperplasia of the zona glomerulosa.

The eight variables used in the analysis were the mean pretreatment values for individual patient plasma concentrations of renin aldosterone, sodium potassium and bicarbonate, together with the mean systolic and diastolic blood pressure values and age. A point of considerable practical importance in this series was that the biochemical features remained unaltered whether the patients were taking a fixed diet of known normal sodium and potassium content, or a free normal diet. Thus data obtained under either of these conditions could be used in the analysis.

The detailed results are shown in Fig. 2 and Table I. Only 5 of the original 31 patients could not be diagnosed from their geometrical positions. All were subsequently correctly placed in the tumor free group by the likelihood ratio criterion. These five patients were all without adenomas, and although their values lay in the area of the overlap of the two quadrics, no patient with adenoma encroached into this zone. Thus, if only the tumor-free quadric was viewed (d_2, Fig. 2) it was seen to contain no patients with an adenoma. This must be regarded as a chance finding and it is not a true geometrical separation. As more patients are added to the series, some with an adenoma will eventually fall within the zone of overlap of the quadrics.

Although eight variables were studied in the initial analysis, separation into tumor and tumor-free groups could still be achieved utilizing the remaining six factors when mean systolic and diastolic blood pressure values were omitted. More strikingly when the mean plasma concentrations of renin and aldosterone were excluded the remaining six variables again permitted separation of the two groups. It should be emphasized however that measurements of both aldosterone and renin are mandatory in the initial diagnostic analysis, the former to make a clear distinction of hyperaldosteronism from other forms of hypertension with mineralocorticoid excess,[17,24-27] the latter to make the

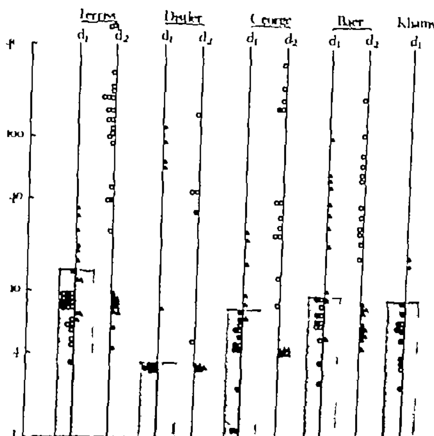


Fig. 2. Values obtained in the internal analyses of the five series of patients for the standardized distances d and d_1 from the centers of the adenoma and tumor-free quadrics, respectively. In the series of Rhamy and associates[11] only the adenoma quadric could be evaluated (see text). Internal analysis II only is shown for data of Distler and colleagues[13] (see Table I). Adenoma patients indicated by circles, tumor free patients by triangles. Shaded zones indicate limits of quadrics.

data of Fig. 1 would be correctly separated by a combination of the geometrical and follow up likelihood ratio approaches.

For quadric analysis in more than one dimension the intervals are replaced by ellipses (in two dimensions) and by ellipsoids or quadrics (in higher dimensions). The frequency curves then become surfaces, and the form of the standardized distances and therefore the shape and orientation of the quadrics then depend on the correlations between the results of different tests as well as on their standard deviations. The likelihood ratio is simply the ratio of the heights of the two frequency surfaces corresponding to the two diseases at the point representing the test result.

While the possibility of separation is obvious in the simple situation of Fig. 1 such a visual assessment becomes increasingly difficult to make as the number of tests increases. There is theoretically no upper limit to the number of dimensions or tests which can be employed in quadric analysis. However it is important that the number of patients in any diagnostic category should exceed the number of tests by at least one (and preferably by more).

These concepts are presented in greater mathematic detail in Appendix 1.

Quadric analysis of the series of Ferriss and associates[12]

The original analysis was retrospective and was confined to 34 patients with hypertension hyperaldosteronism and low plasma renin concentration in whom adequate pathological and biochemical data had been obtained and from whom adrenal tissue was still available for review by the pathologists. The gross and light microscopical features of the adrenal lesions were then assessed by two pathologists working independently of each other and without knowledge of the clinical or biochemical findings. Agreement on the histological diagnosis was not reached in three patients and these were excluded from subsequent consideration. Of the remaining 31 patients

Blood pressure		Standardized distances		Comments on diagnosis
Sys.	Dias.	d	d	
160	110	12 3	64 7	Adenoma by geometry
200	128	16 7	429 0	Outside previous experience, but likelihood-ratio makes adenoma practically certain
192	123	20 4	149 8	
250	140	10 8	171 1	Adenoma by geometry
210	130	32 5	83 6	Outside previous experience, but likelihood-ratio makes adenoma practically certain
190	115	14 4	202 0	
207	114	15 6	691 2	
223	125	9 3	14 1	No renin and aldosterone results available, but diagnosed marginally as non-tumorous

...ments, outpatient readings only were utilized.
...12 mEq. per day) with an abnormally high plasma aldosterone concentration (33 mμg. per 100 ml.) observed after ten days of high
...so widely from those under which renin and aldosterone were measured in other patients.

Quadric analysis applied to other reported series

A further point of interest was to determine if quadric analysis could be successfully applied to other reported data on patients having hyperaldosteronism with and without adrenocortical adenomas. Five papers seemed suitable for such consideration, those of Rhamy and associates,[13] Distler and colleagues,[15] George and co-workers,[17] Baer and associates,[16] and Biglieri and confreres.[11] It must be recognized that with the exception of the paper by Distler and associates[15] (where through the courtesy of Professor H P Wolff we had the opportunity of examining the pathological material) the histological interpretation was not necessarily uniform from one series to another and in particular might well have differed from ours. As is apparent from the fact that unanimity of opinion was not achieved in 3 of our own 34 patients, histological interpretation is by *no means* straightforward in this disease. Three of the five papers[13,16,17] commented on the general tendency for the biochemical disorder to be more severe in the patients with tumors than in the others, although the authors were not able to achieve satisfactory preoperative distinction between the two groups. While the paper by Biglieri and co-workers[11] did not give sufficient details to permit further analysis by us, the remaining four were, in varying degrees, susceptible to quadric analysis, although several problems were raised in the course of these studies

Two separate techniques were applied First, using the various authors data quadrics for the adenoma and tumor-free groups were constructed and the success of the subsequent quadric analysis in separating the diagnostic groups was evaluated This is referred to as an *internal analysis*

Alternatively the circumscribing quadrics already defined in our own series were employed in diagnosing the patients of other investigators in a manner similar to that in which new cases of our own have been evaluated This *external analysis* was seriously limited however by the fact that (with the exception of renin measurement in the paper by Distler and associates[15]) widely differing methods of measuring renin and aldosterone were employed precluding valid comparison of these tests. Moreover as will be seen even the simpler measurements of plasma or serum electrolytes re

*Table II New patients of authors own series diagnosed by quadric analysis**

Patient No	Age	Plasma concentration				
		Na (mEq/L.)	K (mEq/L.)	Bicarbonate (mEq/L.)	Renin (units/L.)	Aldosterone (mµg/100 ml.)
Adenoma confirmed						
N1	48	140 2	2 4	29 6	0 7	31 3
N2	23	146 0	2 6	34 6	0 6	45 0
N3	49	142 6	2 3	36 0	6 2	35 7
N4	35	145 8	2 8	28 0	3 8	24 0
N5	50	143 3	3 2	27 0	9 5	51 0
N6	49	148 0	2 6	35 0	5 3	23 6
N7	39	143 0	2 5	33 6	1 0	192 5
Non-tumorous confirmed						
N8‡	56	142 0	3 7	29 0	—	—

Detailed results of 8 patients added t authors original series since 1970. Values shown are mean values before treatment; in case of bl

‡I this case the diagnosis was made by finding low plasma renin concentration (4.4 units per liter) on the fifth day of low sodium d sodium intake (217 mEq. per day) These values could not be used in quadric analysis, however because the dietary conditions va

differentiation from cases of hyperaldosteronism with elevated renin as may occur in some cases of renal and/or malignant phase hypertension [4 11 17]

Despite this finding that certain of the variables might be omitted from the analysis without impairing the differentiation of tumorous from tumor free patients, it was felt that by considering a greater number of variables a clearer separation of the groups was likely to be achieved thus increasing the reliability of the method in correctly classifying new cases Additional factors might in the future be included

One such variable not considered in the above analysis but perhaps suitable for future inclusion was the preoperative response of the blood pressure to spironolactone [6 7 14 15 16 18] Prolonged preoperative spironolactone had been administered to 17 patients in the tumorous group and to ten of the tumor free group There was a significant hypotensive response in most patients in both groups, one person in each showing no detectable fall of arterial pressure There was no significant difference in the response to spironolactone in the two groups.

It should be emphasized that this was a retrospective assessment, and that the practical value of quadric analysis in distinguishing patients with and without adrenocortical tumor depends on the ability to forecast correctly the diagnosis before operation We have subsequently operated upon 8 further patients with hypertension hyperaldosteronism and low plasma renin concentration 7 of these had an adrenocortical adenoma and one had bilateral adrenocortical hyperplasia. Computer-assisted quadric analysis forecast the result correctly in all 8 cases (see Fig 3 and Tables I and II) Linear discriminant analysis would have misdiagnosed N5 as non tumorous.

As more patients present for diagnosis, it is inevitable that some will fall outside previous experience and thus lie outside both original quadrics. The quadrics should subsequently be adjusted to take account of these new patients once the diagnosis is certain The quadrics will therefore gradually inflate and as a consequence the overlap of the two quadrics will tend to contain increasing numbers of patients, causing likelihood ratio analysis to be utilized more often This feature is in accord with statistical theory which recognizes the likelihood ratio to be a superior form of analysis when dealing with very large groups.

none was diagnosed by geometry alone all lying outside previous experience However subsequent likelihood-ratio analyses in correctly diagnosed all 6 as having adenomas. The reason for this aberration lay in the serum sodium values. The mean values for the two groups are shown below in comparison with the means of our own series

	Ferris and associates (mEq./L.)	*George and associates* (mEq./L.)
Tumor	142 5	145 7
Tumor-free	140 9	143 4

These results suggest important technical differences in the measurement of serum sodium in the two laboratories, and clearly preclude at this time any valid comparison for diagnostic purposes.

Internal analysis. The tumor free group contained only 6 patients, and the quadric construction for that group had therefore to be restricted to a selection of 5 tests. Those used were age, serum sodium potassium, and bicarbonate concentrations, and diastolic blood pressure. All six availabl tests could be employed for the 13 patients with adenoma, and systolic blood pressure was therefore added n the construction of this quadric

With the exception of one tumor-free patient, complete separation was possible from geometric considerations alone. It should be noted that this one patient had bilateral retinal hemorrhages and exudates and in view of the absence of renin measurement, the diagnosis might be held in question.

Use of the likelihood ratio is appropriate only when the numbers of tests making up the two quadrics are equal Systolic blood pressure was eliminated in the tumorous group before proceeding to further assessment of this patient. E en then, this case remained incorrectly assigned.

Baer and associates[29]

External analysis This analysis revealed limitations similar to those seen in the external analysis of the data of George and co-workers.[27] The variables available for comparison with our own data were age, serum sod um potassium and bicarbonate concentrations, and systolic and diastolic blood pressures.

Of the 12 patients with an adenoma, 3 were placed by geometry in the adenoma group the remaining 9 were all also subsequently placed in the adenoma group by likelihood-ratio considerations.

However of the 11 tumor-free patients, 4 were placed by geometry in the adenoma group and all the remaining 7 were also misclassified as tumorous on the basis of likelihood ratio.

As with the data of George and associates,[27] this tendency to misclassify by external analysis was largely due to the higher mean serum sodium and bicarbonate values in the data of Baer and colleagues[29] than in our own

	Ferris and associates (mEq./L.)	*Baer and associates* (mEq./L.)
Tumor		
Na	142 5	146 5
tCO_2	29 64	31 36
Tumor free:		
Na	140 9	142 3
tCO_2	25 60	27 67

In particular the mean serum sodium concentration in the tumor-free cases in the series of Baer and associates[29] closely approximates that found in the adenoma group in our own series.

Internal analysis Since 12 and 11 patients respectively were reported in the tumor and tumor-free groups, full quadric analysis using *all* 7 available tests (age plasma sodium potassium and bicarbonate concentrations, aldosterone excretion and systolic and diastolic blood pressures) could be carried out.

Only two patients in the tumor free group were not clearly diagnosed on geometric grounds. Subsequent likelihood ratio analysis then correctly placed one of these but barely failed to place the other (with odds of 5 to 4 on the adenoma group)

Rhamy and associates[3]

External analysis The patients in the adenoma and tumor free groups were considered in relation to quadrics constructed from our own data using the six tests age serum sodium potassium and bicarbonate concentrations, and systolic and diastolic blood pressures.

Only 5 of the 12 patients in the adenoma

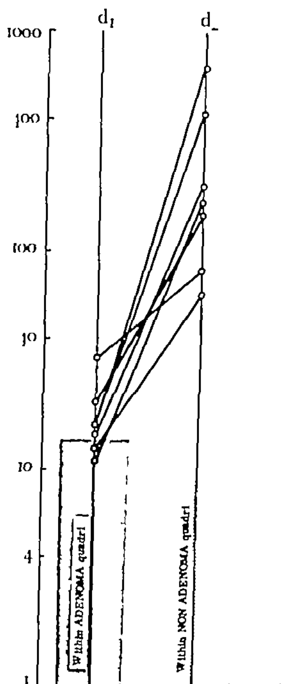


Fig 3 'Standardized distances (d and d_1) for the 7 patients with adenoma added to our original series since 1970 Lines connect values of d and d_1 obtained for each subject. Quadric limits indicated by shaded zones.

sulted in mean values for the adenoma and tumor free groups which differed so markedly from our own means as to suggest important technical variations therefore these measurements occasionally had also to be rejected from use in external analysis.

Despite these reservations, however quadric analysis of these several papers, which will be considered in turn produced interesting results (Table I and Fig 2)

Distler and associates[13]

External analysis Because aldosterone secretion was estimated *in this series, these* results could not be compared with the plasma aldosterone concentration measurements of our study In addition although the same technique of measuring plasma renin concentration was employed minor variations in the normal range quoted again suggested that direct comparison would be of doubtful validity Finally precise figures for plasma bicarbonate were not given External *quadric analysis using the* data of Ferriss and co-workers[22] for comparison had therefore to be restricted to the values for age serum sodium and potassium concentrations, and to systolic and diastolic blood pressure values.

All 5 patients with an adrenocortical adenoma were correctly placed by the geometric method but only 1 of the 5 tumor free patients was correctly placed by geometry Of the remaining 4 tumor-free patients, subsequent likelihood ratio analysis failed to place 3 correctly

Internal analysis Because of the limited number of patients (5) in each diagnostic group it was necessary to restrict the number of tests to 4 in the construction of quadrics. Three separate selection groupings were used (1) serum sodium and potassium plasma renin concentration aldosterone secretion rate (2) serum sodium and potassium systolic and diastolic blood pressures and (3) serum sodium and potassium aldosterone secretion rate diastolic pressure All three selections produced pairs of quadrics which completely separated the groups on geometrical considerations alone (Fig 2 and Table I)

George and associates[27]

External analysis An attempt was made to classify the patients of this series, using the quadrics established for our own series, and these available variables—age serum concentrations of sodium potassium and bicarbonate and systolic and diastolic blood pressures.

Of the 13 patients with an adenoma 3 were diagnosed correctly by geometry alone The remaining 10 gave values outside our previous experience, but the likelihood ratios indicated all 10 had an adenoma.

Of the 6 patients without an noma,

none was diagnosed by geometry alone all lying outside previous experience. However subsequent likelihood ratio analysis incorrectly diagnosed all 6 as having adenomas. The reason for this aberration lay in the serum sodium values. The mean values for the two groups are shown below in comparison with the means of our own series

	Ferriss and associates ($mEq./L.$)	*George and associates* ($mEq./L.$)
Tumor	142 5	145 7
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Internal analysis The tumor-free group contained only 6 patients, and the quadric construction for that group had therefore to be restricted to a selection of 5 tests. Those used were age, serum sodium, potassium and bicarbonate concentrations, and diastolic blood pressure. All six available tests could be employed for the 13 patients with adenoma, and systolic blood pressure was therefore added in the construction of this quadric.

With the exception of one tumor free patient, complete separation was possible from geometric considerations alone. It should be noted that this one patient had bilateral retinal hemorrhages and exudates and in view of the absence of renin measurement the diagnosis might be held in question

Use of the likelihood-ratio is appropriate only when the numbers of tests making up the two quadrics are equal. Systolic blood pressure was eliminated in the tumorous group before proceeding to further assessment of this patient. Even then this case remained incorrectly assigned

Baer and associates[16]

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Only two patients in the tumor free group were not clearly diagnosed on geometric grounds. Subsequent likelihood-ratio analysis then correctly placed one of these but barely failed to place the other (with odds of 5 to 4 on the adenoma group)

Rhamy and associates[13]

External analysis. The patients in the adenoma and tumor-free groups were considered in relation to quadrics constructed from our own data using the six tests age serum sodium potassium and bicarbonate concentrations, and systolic and diastolic blood pressures.

Only 5 of the 12 patients in the adenoma group were...

geometric position these lying inside the adenoma quadric. The remaining 7 were beyond our previous experience lying outside both quadrics, but subsequent application of the likelihood ratio criterion diagnosed all but one as tumorous

The data from the 2 tumor-free patients also lay outside our experience the likelihood ratio criterion placing them incorrectly in the adenoma group

Internal analysis Full analysis was not possible since a valid quadric could not be drawn for the two patients in the tumor free group It was possible however to construct a quadric for the adenoma cases and to see where the tumor free patients lay in relation to it This was done and it was found that both tumor free patients lay well outside the adenoma quadric.

Discussion

In this article we have applied the technique of computer assisted quadric analysis to the differential diagnosis of five series of hypertensive patients with aldosterone excess and either presumed or demonstrated low plasma renin We have shown that diagnostic criteria for the distinction of patients with and without adrenocortical adenoma established in a retrospective analysis of 31 of our own patients have permitted the correct forecast preoperatively in all of 8 later patients of our own 7 of whom were found to have an adrenocortical adenoma and one of whom had micronodular hyperplasia.

We have also applied similar principles to four other published series of cases and have shown that differential diagnosis could be achieved in these also with a high incidence of success An interesting point to emerge from these further analyses, however was the need to establish valid quadrics by internal analysis of each series separately External analysis, using the quadrics delineated in our own patients was much less successful While it might have been expected that important methodological differences between one laboratory and another with regard to complex measurements such as those of renin and aldosterone would limit the use of these variables in quadric analysis, the major differences observed between our own mean values for plasma sodium and those reported by George and associates[17] and by Baer and coworkers[30] were more surprising Clearly however the long range diagnosis of an individual case by reference to quadrics established in another center is open to considerable error unless care is taken to standardize even the simpler biochemical measurements made by the laboratories concerned and to adjust the mean values accordingly

The success of quadric analysis in the differential diagnosis of hyperaldosteronism raises several further interesting but as yet unresolved points. If as seems possible the fundamental lesion is caused by aldosterone excess, and the other biochemical features all generally more severe in the patients with adenoma stem from this, it is perhaps surprising that inclusion of these presumably secondary features should in a compound form of analysis add precision to diagnosis, as they undoubtedly do It may be that relatively greater accuracy can be achieved with more commonly performed tests, such as plasma sodium and potassium measurement despite the interlaboratory variation suggested in the preceding paragraph Alternatively there could here be an indication of different responsiveness of tissue to aldosterone excess in the two groups.

We have found no evidence that the patients without adrenocortical adenoma represent a milder and earlier form of the disease The mean systolic and diastolic blood pressures were closely similar in the two groups. Moreover in 3 of the 5 series under consideration[11,13,22] patients harboring an adrenocortical adenoma had a lower mean age than those without while the mean ages were closely similar in the two remaining series.[30,37]

In our view the success of computer assisted quadric analysis in this differential diagnostic problem represents a considerable advance in the management of patients with hyperaldosteronism and low plasma renin In the patients without adenoma in particular the physician is now in a position to offer long term or even definitive spironolactone therapy[4,7,11,14,19] as a valid alternative to the extensive bilateral adrenal resection which is needed to correct this form of the disease surgically

More generally the application of quad

ric analysis to other areas of medical diagnosis and prognosis holds considerable promise for future work.

Summary

Retrospective assessment by means of computer-assisted quadric analysis of a series of 31 patients with aldosterone excess and low plasma renin permitted complete separation into two groups—those with and those without adrenocortical adenoma.

Application of these principles to 8 more patients was successful in all cases in correctly diagnosing the type of pathological lesion before operation.

Study of four similar published series has shown that each of these could also be accurately differentiated into the two diagnostic categories by quadric analysis. However probably because of interlaboratory variation internal analysis using circumscribing quadrics established for each series individually was much more reliable than external analysis with reference to the quadrics of the original series.

Quadric analysis, by enabling a confident prediction to be made before operation as to the presence or absence of an adrenocortical adenoma, has major value in the practical management of these patients. In particular in the cases without adenoma, long term or definitive spironolactone therapy may now be offered as a valid alternative to extensive bilateral adrenal resection.

It is further suggested that the technique of quadric analysis is likely to have wide application in other diagnostic areas.

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Appendix I

Diagnosis by quadric analysis Suppose that a number of patients have been diagnosed into two disease groups, 1 and 2 and that for each patient the results of t diagnostic tests are available Let G_1 and G_2 denote the two classes of vectors of test results. Let $\bar{x}_i$ be the vector of t means and S_i the covariance matrix of the ith group of patients ($i = 1\ 2$) For any t-dimensional vector x define the two quadratic forms

$$d_i(x) = (x - \bar{x}_i)' S_i^{-1} (x - \bar{x}_i)$$

and let

$$k_i = \max_{x \in G_i} d_i(x)$$

Then

$$Q_i = \{x : d_i(x) \leq k_i\} \quad (i = 1, 2)$$

defines the circumscribing quadrics of the two groups.

The degree of separation of the two groups can then be investigated in two stages (1) by geometrical considerations, and (2) by estimated likelihood ratio.

Stage 1 Any x in G_1 such that $d_2(x) > k_2$ or any x in G_2 such that $d_1(x) > k_1$ is said to be separated by geometrical considerations alone. Any x in G_1 or G_2 not so separated lies in $Q_1 \cap Q_2$ the intersection of the two quadrics.

Stage 2 Any x in G_1 or G_2 not separated by (1) may be investigated by consideration of the estimated likelihood ratio

$$\Lambda(x) = (\det S_2/\det S_1)^{1/2} \exp\{-\tfrac{1}{2}[d_1(x) - d_2(x)]\}$$

where det ( ) denotes determinant. Our rule for this study was to regard x in G_1 as separated if $\Lambda(x) > 1$ and similarly x in G_2 as separated if $\Lambda(x) < 1$

For the diagnosis of a new patient with vector x of test results compute $d_1(x)$ and $d_2(x)$ If $d_1(x) \leq k_1$ and $d_2(x) > k_2$ then x lies in Q_1 but outside Q_2 and the diagnosis is disease 1 If $d_1(x) > k_1$ and $d_2(x) \leq k_2$, then x lies in Q_2 but outside Q_1 and the diagnosis is disease 2 If $d_1(x) \leq k_1$ and $d_2(x) \leq k_2$ the patient is in both Q_1 and Q_2 compute $\Lambda(x)$ and diagnose as disease 1 or 2 according as $\Lambda(x) > 1$ or < 1 If $d_1(x) < k_1$ and $d_2(x) > k_2$ the new patient is outside previous experience in this case again compute $\Lambda(x)$ and diagnose as above.

Notes 1 The number of patients in each group must be at least $t + 1$ If the number of patients is exactly $t + 1$ then the generalized distance value $d(x)$ is $t^2/(t + 1)$ for every patient in the group

2 Separate covariance matrices are computed for the two groups. Experience with this syndrome and other diseases suggests that the covariance matrices are sufficiently different to make linear discriminant analysis of inferior quality

3 Experience since 1970[illegible] together with some empirical and theoretical studies, suggests that we would now place more emphasis on the estimated likelihood ratio $\Lambda(x)$ while retaining the geometric approach largely for the visual insight it provides.

4 For test results which have a very skew distribution it may be advisable to use logarithms of the results.

5 For a statistical analysis which depends on the likelihood ratio alone, see Smith[illegible] for an alternate geometric approach see Kendall.[illegible]

Case reports

Electrocardiographic changes in acute pancreatitis resembling acute myocardial infarction

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Rarely patients with pancreatitis present with electrocardiogram (ECG) changes indistinguishable from those of acute myocardial infarction. While the majority of these patients have manifested severe pancreatitis terminating in shock and death,[1-4] two have presented with clinically milder pancreatitis and have survived.[5,6] In each case no evidence of coronary occlusion was demonstrated either at autopsy,[1-4] by coronary arteriography,[5] or by the transient nature of the ECG changes in the absence of other clinical evidence of myocardial infarction.[6] The present report concerns the second documented patient with acute pancreatitis, transient ECG changes of acute myocardial infarction, and normal coronary arteries demonstrated by coronary angiogram.

Case report

D. I., a 41-year-old Negro man, was admitted to the Veterans Administration Hospital, Washington, D. C., on Aug. 5, 1969, because of epigastric pain, nausea, and vomiting following a 3 day period of markedly excessive alcohol consumption. The patient was a chronic alcoholic whose past history revealed several episodes characterized by similar though less severe symptoms. He denied chest pain, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, or ankle edema. Physical examination revealed a thin Negro man with a blood pressure of 110/70 mm. Hg, a pulse of 90/minute and regular, and temperature of 99°F. There was no asterixis and no physical findings of cirrhosis. Cardiac examination revealed the left ventricular impulse to be in the fifth intercostal space in the midclavicular line. There were no murmurs or gallops. Abdominal examination revealed right upper quadrant tenderness with the liver palpable 2 cm. below the right costal margin. The remainder of the physical findings were within normal limits. Laboratory findings on admission were a hematocrit of 40, white blood cells 12,000 per cubic millimeter with a normal differential. Blood urea nitrogen was 15 mg. per 100 ml., sodium 138 mEq. per liter, potassium 4.4 mEq. per liter, chloride 94 mEq. per liter, and CO_2 content 25 mEq. per liter. Calcium was 8.6 mg. per 100 ml. and phosphorus 3.3 mg. per 100 ml. Amylase was 250 Somogyi units per 100 ml. Liver function tests revealed a bilirubin of 1.2 mg. per 100 ml., alkaline phosphatase 8 King-Armstrong units, serum glutamic oxalacetic transaminase (SGOT) 60 Karmen units, serum glutamic pyruvic transaminase (SGPT) 260 Karmen units, total protein 6.0 Gm. per 100 ml., albumin 3.0 Gm. per 100 ml., cephalin flocculation 4+ at 48 hours, and a Bromsulphalein (BSP) of 5 per cent. Coombs test was negative and a 2 hour postprandial blood glucose was 76 mg. per 100 ml. The patient was treated with intravenous hydration and prochlorperazine for nausea. Symptoms subsided over the next 24 to 36 hours. Repeat blood studies done the day after admission showed a serum amy-

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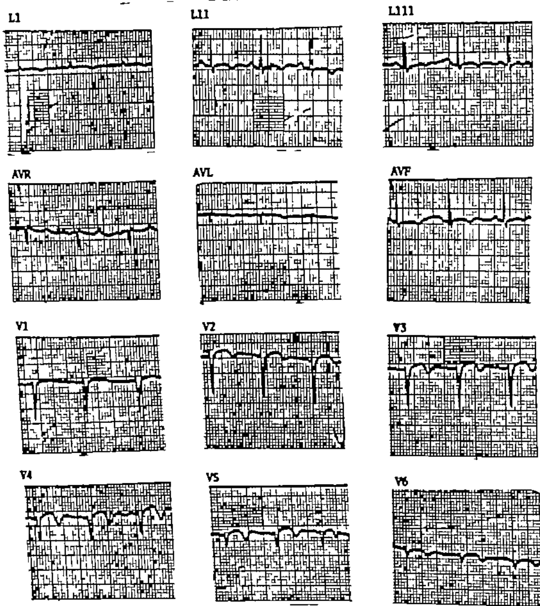


Fig. 1A Admission ECG showing changes consistent with anterolateral wall myocardial infarction.

lase of 116 Somogyi units per 100 ml., SGOT 45 Karmen units, and SGPT 19 Karmen units. Radiologic examination of the chest and abdomen were negative as was an upper gastrointestinal tract series and gallbladder series. Liver biopsy showed eosinophilic infiltration of one portal triad. There was no evidence of cirrhosis. ECG done on the day of admission (Aug. 5 1959) was characteristic of an acute anterior myocardial infarction (Fig. 1A). Three days later there was return of anterior forces in the precordial leads. The "T" waves were still inverted in Leads I, II III V_L, V and V_{4-6} (Fig. 1B). Throughout the remainder of the patient hospital course the "T" waves remained inverted in the precordial leads. A subsequent ECG on May 11 1970, showed normalization of the "T" waves in the precordial leads with nonspecific "T" wave changes in the limb leads (Fig 1C). Coronary arteriography was performed on Aug. 20, 1970, and demonstrated normal coronary arteries (Fig. 2)

Discussion

Transiently occurring QRS changes simulating myocardial infarction have been reported in a variety of clinical conditions.

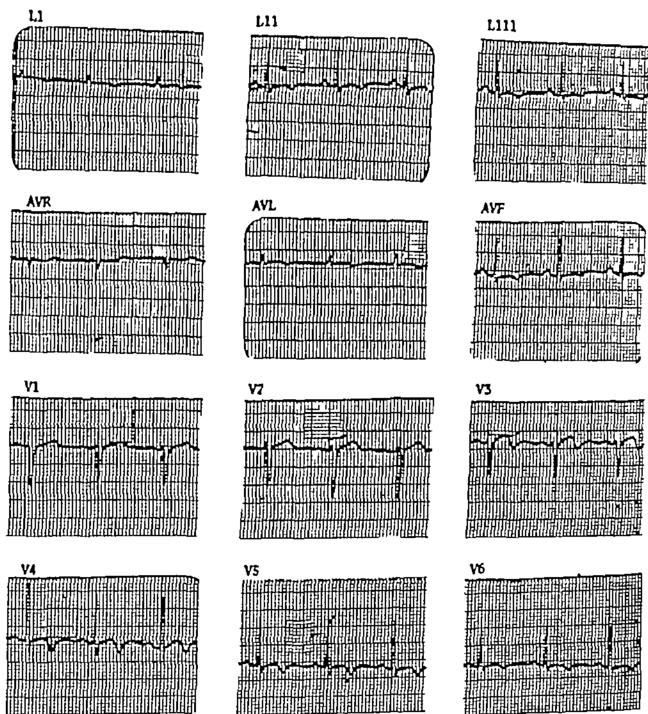


Fig. 1B. ECG 3 days after admission showing recovery of anterior forces. "T" wave changes are still present.

The common denominator in many of these cases has been the occurrence of severe metabolic or hemodynamic dysfunction usually manifested by shock.[7] In patients in shock a possible etiology for the QRS changes seen on ECG's is temporary myocardial ischemia. Thus Q waves have been seen transiently in patients with angina[8] and in experimental situations following temporary occlusion of a coronary artery.[9] In the presently reported patient, and in the 2 previously reported patients with pancreatitis and ECG changes who survived, shock was not a feature. These patients presented with mild pancreatitis and made uneventful recoveries. The ECG abnormalities observed in these latter patients have been felt by previous authors to be secondary to myocardial necrosis either through a direct effect of pancreatic proteolytic enzymes or through vagus mediated reflexes producing suf

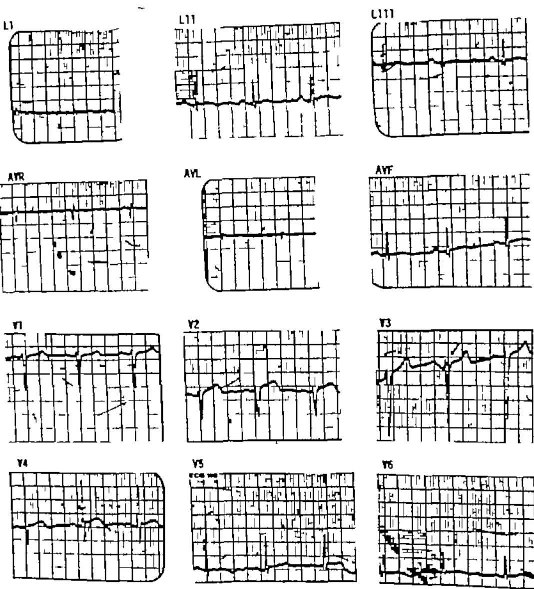


Fig. 1C Anterior forces remain normal ith further normalization of previously noted "T" wave changes.

ficient disturbance in cardiac rate or rhythm to yield cell death. However myocardial necrosis following intravenous injection of proteolytic enzymes is long lasting with resolution occurring n about 2 weeks.[10] The return of the QRS complex to normal in 3 days in our patient and in 36 hours in the patient described by Spritzer and coworkers[1] would seem too short for the healing of myocardial necrosis. It is possible however that proteolytic agents in lower concentration, or lipases, or phospholipolytic enzymes released by the inflamed pancreas[11] might produce sublethal damage to myocardial cells resulting in only transient and potentially rapidly reparable changes in the myocardial plasma membrane. This would lead to a transient leak of potassium with local hyperkalemia. If this local potassium elevation occurred to a degree sufficient to lower the resting potential of surrounding myocardial cells below threshold potential no depolarization would occur A parallel to this situation



Fig 2A Selective left coronary arteriogram. Left anterior oblique projection showing normal coronary vessels.



Fig 2B Selective right coronary arteriogram. Left anterior oblique projection showi g normal coronary vessels.

might occur in acute myocardial infarction. Release of potassium from necrosing cells has been demonstrated to result in failure of depolarization of surrounding viable myocardial cells. These local changes in potassium concentration may occur without any change in the systemic serum potassium concentration.[12]

Thus in patients with pancreatitis and transient ECG changes of myocardial infarction the observed electrical silence on ECG might result from transient cell membrane changes in otherwise viable myocardial cells which when repaired result in normal depolarization and propagation of the action potential.

Summary

A patient with acute pancreatitis of moderate severity showing transient ECG changes indistinguishable from those of acute myocardial infarction is being described. The patient had neither shock nor electrolyte imbalance. Recovery was uneventful. The major ECG abnormalities returned to normal within 3 days. Selective coronary arteriogram was normal. Local electrolyte derangement with membrane potential alterations inducing transient electrical silence is the most likely explanation.

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Anastomotic coronary vessels in hypoplasia of the right ventricle

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We were recently confronted with a unique heart in which the tricuspid valve was atretic, the pulmonary valve was undeveloped and incompetent, the proximal pulmonary artery was deformed and aneurysmal, and a tumoral mass of atypical vascular channels occupied the interventricular septum. In considering the nature of these vessels, we reviewed all cases of tricuspid and pulmonic atresia at our disposal, and we will discuss the range of abnormality in the coronary vasculature when associated with these defects.

Case report

At 14 hours of age, the patient developed cyanosis which worsened and was accompanied by increasing tachypnea. Cardiac catheterization on the second day revealed tricuspid atresia. Angiocardiography showed right atrial dilatation and filling of the pulmonary arteries through a patent ductus arteriosus. The right ventricle was not visualized. A right subclavian to right pulmonary artery anastomosis was performed but within a few hours intense cyanosis recurred. An anastomosis of the descending aorta to the left pulmonary artery was created, but the infant developed progressive respiratory distress with acidosis and died 24 hours after the second procedure on the third day of life.

Autopsy. The infant weighed 3,000 grams and was normally developed, with the exception of the heart and great vessels. The lungs were hemorrhagic and edematous with focal hyaline membranes and acute lobular pneumonia. The heart weighed 22 grams (expected normal[1] is 21 grams) and had normal situs, with the apex, composed of hypertrophied left ventricle, pointing inferiorly to the left. The right atrium was markedly dilated and the tricuspid ring was atretic. The fossa ovalis measured 1 cm. in diameter and was covered by a freely mobile septum primum. The right ventricle consisted of a narrow infundibular chamber 1.5 cm. long, occupying the anterior base of the heart. The wall was 1.0 cm. thick and the endocardium was opaque and gray. Multiple fine irregular trabeculae converged from the right ventricular endocardium on a point on the posterior wall at the junction with the pulmonic valve ring (Fig. 1). The valve cusps were absent but there were some irregular fibrous trabeculae on the endothelial surface. Arising from the right side of the dilated main pulmonary artery at its base, there was a huge saccular aneurysm measuring 1.2 cm. long by 1.5 cm. wide (Fig. 1). It lay above and to the right of the right ventricle, anteromedial and adherent to the right atrial appendage, and anterior to the aorta. The wall of the aneurysm was identical in appearance and thickness to the main pulmonary artery, except posteriorly where irregular folds on the endothelial surface suggested abortive cusp development (Fig. 1). Distal to the aneurysm the main pulmonary artery had a diameter of 1 cm. for the next 0.8 cm. It then dilated to 2 cm. diameter at the junction with the ductus arteriosus, which was 0.5 cm. long with an internal diameter of 0.1 cm.

The left atrium was unremarkable and the mitral valve was dilated to 4.0 cm. in circumference but was normally formed. The left ventricle was hypertrophied with muscle thickness of 0.7 cm. when measured 1 cm. below the posterior leaflet of the mitral valve. The outflow tract of the left ventricle was narrowed by a mass of yellowish-gray tissue

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Fig. 1 Anterior aspect of the heart showing saccular aneurysm at the root of the pulmonary trunk. A Unopened B open arrows show abortive semilunar cusp development. Note thickness of myocardium.

hat occupied the entire interventricular septum from just below the aortic valve to the inferior margin of the heart (Fig. 2) It measured 2.4 by 1.8 by 1.6 cm. and consisted of soft, irregular nodules with multiple narrow clefts (Fig. 2) The mass was covered by endothelium but section revealed no encapsulation, as the abnormal tissue merged imperceptibly into adjacent brown myocardium of the right and left ventricles. Our impression of the mass at the time of dissection was localized rhabdomyoma or fibroma. There was no gross communication between the two ventricles through the septum. The aortic valve circumference was 1.2 cm. Three normal cusps ere present and the coronary arteries arose as usual in the sinuses of Valsalva. Their proximal branches ere not remarkable and soon tapered to the usual small dimensions of newborn. The aorta ascended and arched in normal fashion, giving rise to the usual three brachiocephalic vessels. The right subclavian artery was thrombosed t its origin, nullifying the Blalock-Taussig procedure, but the Pott anastomosis was patent.

Histologic study Histologic examination of the septal mass revealed multiple endothelial-lined channels with irregularly thick walls of abundant collagen and acid mucopolysaccharide, a few irregularly disposed thin elastic fibers, and no smooth muscle (Fig 3) The channels were often separated by thin fascicles of myocardium and they communicated in different areas with myocardial arterioles, with larger arterial branches near the epicardial surface, and with the right ventricular chamber whose endothelial lining was composed of the same thick but minimally elasticized connective tissue. The wall of the pulmonary artery aneurysm was composed of irregular bundles of elastic and collagen fibers, with increased ground substance and only a few scattered smooth muscle fascicles. Similar tissue was found between the right ventricular myocardium and the root of the main pulmonary artery The normal arterial arrangement of concentric longitudinal elastic laminae in the media with alternating bands of smooth muscle did not begin until approximately 1 0 cm. distal to the ventricle.

Discussion

The mass of atypical vascular channels in the ventricular septum may have originated as a hamartoma a primary malformation of developing intramyocardial vessels, or as a secondary response to the physiological consequences of the other cardiac malformations. In favor of the first alternative is the similarity of the vessel structure in the case reported by Franciosi and co-workers. A mass was resected from the apex of a child's heart having no other congenital malformations. It was composed of tortuous channels that communicated with branches of the left anterior descending coronary artery as demonstrated by cineangiography In the absence of other developmental abnormality the authors use of the term vascular hamartoma to describe this lesion is quite

appropriate. A comparable malformation was described in an autopsy by Lovitt and Lutz.[3]

However, certain features of the atypical vascular channels in our case are similar to normal intramyocardial channels, suggesting that the second possibility ought to be considered. Arteriosinusoidal and arterioluminal communications in normal adult hearts were demonstrated by Wearn and associates,[4,5] who injected coronary arteries with opaque media. The channels are most prevalent in the anterolateral surface of the right ventricle and are composed of an endothelial lining with a thin connective tissue supporting layer. Presumably they are available to dilate and expand in case of a physiological stimulus such as would be provided by pulmonic atresia in association with a competent tricuspid valve or by pulmonary insufficiency. Retrograde flow from the ventricle has been demonstrated through one such fistula by cineangiography.[6] The circumstance in which secondary enlargement of arterioluminal communications is most often described is pulmonic valvular atresia coupled with a competent tricuspid valve, which produces high pressure in the right ventricle.[7,8] An excess of collagen and elastic fibers plus ground substance together with diminution in smooth muscle have been described by Grant[9] and Kauffman and Andersen[10] in anastomotic channels in hearts with pulmonic atresia.

Very similar histologic alterations were



Fig. 2A. Left ventricle. The ventricular septum at the left is bulging into the subaortic outflow tract of the left ventricle. Endothelium covers the vascular malformation.



Fig. 2B. Section reveals multiple slits throughout the yellowish-gray mass.

Fig. 3A The malformed vascular channels in the wall of the right ventricle and ventricular septum are shown. The low-power view demonstrates the large number and irregular pattern of the vessels, which are separated at times by thin strands of myocardium. (×30.)



Fig. 3B Higher magnification shows connective-tissue hyperplasia and absence of smooth muscle. (Masson trichrome stain, ×250.)

well shown in the coronary arteries of three patients with pulmonic atresia and one with aortic atresia by Oppenheimer and Esterly.[11] They considered the lesions to represent an acquired degenerative process of occlusive endarteritis affecting the coronary artery supplying the hypoplastic ventricle. Anastomoses to the ventricular chamber were not demonstrated.

Twelve additional cases of tricuspid or pulmonic valvular atresia with hypoplasia of the right ventricle in our collection were reviewed. In two specimens with pulmonic atresia coronary artery—right ventricle anastomoses were demonstrable. The vascular communications in these cases varied from a grossly identifiable origin from a main coronary artery to microscopically demonstrable direct arterioluminal anastomoses to enormous proliferation and disorderly ramification of deformed vessels whose identification and connections required serial histologic study. Despite enormous differences in their gross manifestations each set of anastomosing channels shared certain histologic features, that is, the normal arrangement of intima, media, and adventitia was replaced by a haphazard array of elastic and collagen fibers and smooth muscle was missing. The abundance of acid mucopolysaccharides in the angiomatous vascular malformation of the septum was superimposed on the distorted architecture common to all cases.

Grant[8] considered an aneurysmal coronary anastomosis to have a developmental origin in conjunction with malformation of the bulbus cordis, whereas Oppenheimer and Esterly[11] suggested disuse atrophy as a possible mechanism of the coronary artery changes in their cases. But because most cases of pulmonic and aortic atresia are not associated with such lesions, they concluded that neither the valvular malformation nor the coronary lesion was responsible for the other. Without extensive sequential anatomic study of similarly affected fetal hearts or of experimental creation of a comparable malformation one can only speculate about the pathogenesis of the lesion. Yet it seems reasonable to assume that in some instances the intramyocardial channels normally joining the coronary arteries to the ventricular chambers may enlarge, thicken, and become exceedingly tortuous when blood in the chamber has no other outlet.

The aneurysm of the proximal pulmonary artery was associated with complete agenesis of pulmonic valvular tissue. This malformation has not been heretofore described in association with tricuspid atresia. Except with ventricular septal defect often accompanied by pulmonic stenosis, the pulmonic valve is rarely absent from a patent vessel.[13,13] A saccular aneurysm of the artery and absence of the pulmonic valve have been described in an adult with Marfan's syndrome[14] and marked generalized dilatation of the trunk is frequent when the pulmonic valve is absent.[13,14] In reviewing the histopathology of three specimens with aneurysmal dilatation of the pulmonary trunk associated with absence of the pulmonary valve cusps, Miller and associates[14] found that the base of the artery was separated from its normal insertion in the myocardium of the conus by valvular sinus tissue lacking in smooth muscle. The same was true in our case and it would appear to provide the opportunity for marked dilatation of the pulmonary trunk. Blood that regurgitated from the pulmonary artery through the common orifice of the valve and aneurysm into the right ventricle may have stimulated the development of the vascular channels in this remarkable specimen.

Summary

A unique heart with tricuspid atresia, absence of the pulmonic valve, an aneurysm of the base of the pulmonary artery, and a pseudoneoplastic mass of deformed vascular channels in the ventricular septum was described. Histopathologic study of the vessels revealed them to be anastomoses between the normal coronary arterioles and the hypoplastic right ventricle, so their development is attributed to an unusual degree of hyperplasia of normal intramyocardial communications in response to the physiological stimulus of blood regurgitated through the congenitally incompetent pulmonic valve.

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Review

Comparison of therapeutic effects of coronary drugs in the USSR

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The prevalence of coronary artery disease in urban Union of Soviet Socialist Republics (USSR) population appears to be similar to that in Western European countries and the United States and therefore is a problem of major concern Numerous articles proceedings of conferences and monographs on coronary heart disease appeared during the past decade Naturally drug therapy plays a substantial part as demonstrated in the articles by Goldberg [1] Doshitsyn and co-workers[2] and in the monographs of Kissin[3] and Votchal [4] However there does not seem to be a project in the USSR comparable in scale to the National Institutes of Health supported Coronary Drug Project. In the United States a massive double-blind therapeutic trial of lipid lowering drugs in coronary disease is in progress. This study known as the Coronary Drug Project has 8 341 male myocardial infarction patients enrolled in 55 centers throughout the country At the time of enrollment they were between the ages of 30 and 64 years. The drugs under study are nicotinic acid clofibrate (Atromid S) estrogen D thyroxine (Coloxin) and placebo The duration of follow up is set at five years. Events studied include recurrent myocardial infarction acute coronary insufficiency angina and other manifestations of arteriosclerosis, such as electrocardiographic changes, serum lipids and mortality rates. The study will have completed five years for all patients by 1974 and should answer the question whether such drugs are useful in the therapy of arteriosclerosis particularly coronary arteriosclerosis. The large control group of patients will provide in valuable information on the natural history of male coronary patients, a necessary yardstick for comparison with coronary patients treated by any means.

One of the best controlled recent studies is the comparison of the therapeutic effect of several drugs used in the USSR for treatment of coronary heart disease by Votchal and Goldberg[5] of the Central Institute of Postgraduate Medical Education in Moscow

In double-blind technique the therapeutic effect of preparations—Papaverin Nospa * Segontin † Ustimon,‡ Intensain §

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*Nospa (Chinoin, Budapest) isodihydroperparine hydrochloride.

†Segontin (Chinoin, Budapest) (N 3'-phenyl-propyl-(2'))-1 1-diphenyl propyl (3)-amine. Identical preparation "Diphril" reproduced in Chemical-Pharmacol. Institut of Leningrad, USSR.

‡Ustimon (Oesterr Stickstoffwerke, Austria, reproduced in Chemical-Pharmacol. Instit t of Leningrad, USSR) 3,3'-[ethylenebis (methylimino)] dipropylbis (3 4,5-trimethoxybenzoat) Reproduced in Institut of Acad. Sci. Latvian, SSR.

§Intensain (Casella-Riedel Pharma, Frankfurt. West Germany) 3(β-Diethylamino-ethyl)-4-methyl-7 Carbethoxy-methoxy 2-oxo(1,2-chromen)-hydrochloride (reproduced Pliva, Yugoslavia).

Table I

Drug	*Dosage (mg)*	*Mean latent period (days)*	*No. of patients*	*No. of cases with side effects*	*Angina attacks per day decreased*		
					from	*to*	*p*
Papaverin	300	3 3	107	4 (mild)	3 9	2 8	<0 05
Nospa	160-240	2 7	54	0	3 2	1 6	<0 003
Segontin	90-180	2 3	135	6 mild, transient	3 7	1 2	<0 001
Ustimon	240-360	3 1	65	2	3 6	1 9	<0 003
Intensain	450	1 9	22	None, if taken after meal	3 6	1 9	<0 003
Isoptin	120-140	1 9	69	1 mild, transient	3 2	1 3	<0 001

Table II

Drug	*Per cent of patients*				
	Favorable results	*Complete abolishment of angina*	*Improvement in ECG*	*Most effective drug for each group*	*Only effective drug for each group*
Papaverin	63 5 ± 4 5	18 7 ± 3 8	12 6 ± 3 4	7 4 ± 2 5	1 1 ± 1 0
Nospa	72 2 ± 6 1	33 3 ± 6 4	21 7 ± 6 1	25 9 ± 5 9	5 6 ± 2 8
Segontin	77 8 ± 3 6	48 1 ± 4 3	38 8 ± 4 5	44 4 ± 4 3	12 1 ± 2 8
Ustimon	72 3 ± 5 6	36 9 ± 5 9	26 8 ± 5 9	35 4 ± 5 9	7 7 ± 3 3
Intensain	77 3 ± 8 9	50 0 ± 10 5	38 0 ± 10 6	38 1 ± 10 3	14 3 ± 7 5
Isoptin	87 0 ± 4 1	47 8 ± 6 0	38 1 ± 6 1	50 7 ± 6 0	17 4 ± 4 6

Isoptin and placebos—were compared in 172 patients with ischemic heart disease. The use of these drugs is not limited to the USSR in fact, there is a substantial Western literature about these preparations which is not reviewed here. It was thought that a brief review of the Russian investigations would be of interest, in context with the extensive research elsewhere, because of the limited accessibility of Russian publications. Not all preparations were used in all patients, but the subgroups were similar as to age sex distribution, and severity of disease. Papaverin was used for those patients where discontinuation of some therapy was clinically not advisable. However in some patients with frequent and severe angina attacks, not controlled by Papaverin, the comparison was limited to the other five drugs. Consequently the subgroups were not of identical size, but this does not invalidate the statistical analysis.

The authors are aware of the controversial literature on the therapeutic effect of Papaverin in the past six decades, but believe this may have been due, in part, to the different dosage used varying from 60 to 400 mg per day The authors used Papaverin in a dosage of 300 mg—in general they also used rather large doses of the other five preparations. Number and frequency of angina attacks and electrocardiogram (ECG) changes (resting and Master's exercise tests, 12 conventional and 3 Nehb leads) served as criteria.

The cycles of treatment ranged from about one to four weeks. Thus, long-term effects, such as the promotion of growth of

*Isoptin (Knoll A. G. Ludwigshafen, West Germany) α-isopropyl-α-[(N-methyl-N-homoveratryl)-γ-aminopropyl]-3,4-dimethoxyphenylacetonitrile (beta-blocking).
Segontin, Ustimon, and Intensain were used in the chemically identical substitute preparations. Obviously no similar preparation has been developed in the USSR.

Review

Comparison of therapeutic effects of coronary drugs in the USSR

Ernst Simonson M D
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The prevalence of coronary artery disease in urban Union of Soviet Socialist Republics (USSR) population appears to be similar to that in Western European countries and the United States and therefore is a problem of major concern Numerous articles proceedings of conferences and monographs on coronary heart disease appeared during the past decade Naturally drug therapy plays a substantial part as demonstrated in the articles by Goldberg [1] Doshitsyn and co-workers[2] and in the monographs of Kissin[3] and Votchal [4] However there does not seem to be a project in the USSR comparable in scale to the National Institutes of Health supported Coronary Drug Project In the United States a massive double-blind therapeutic trial of lipid lowering drugs in coronary disease is in progress This study known as the Coronary Drug Project has 8 341 male myocardial infarction patients enrolled in 55 centers throughout the country At the time of enrollment they were between the ages of 30 and 64 years The drugs under study are nicotinic acid clofibrate (Atromid S) estrogen D thyroxine (Coloxin) and placebo The duration of follow up is set at five years. Events studied include recurrent myocardial infarction acute coronary insufficiency angina and other manifestations of arteriosclerosis, such as electrocardiographic changes, serum lipids and mortality rates. The study will have completed five years for all patients by 1974 and should answer the question whether such drugs are useful in the therapy of arteriosclerosis particularly coronary arteriosclerosis The large control group of patients will provide in valuable information on the natural history of male coronary patients, a necessary yardstick for comparison with coronary patients treated by any means

One of the best controlled recent studies is the comparison of the therapeutic effect of several drugs used in the USSR for treatment of coronary heart disease by Votchal and Goldberg[5] of the Central Institute of Postgraduate Medical Education in Moscow

In double blind technique the therapeutic effect of preparations—Papaverin Nospa * Segontin † Ustimon,‡ Intensain §

From Mount Sinai Hospital, Minneapolis, Minn.
Supported in part by grant HE 07010.
Reprint requests to Dr Ernst Simonson, Mount Sinai Hospital, 2215 Park Avenue Minneapolis Minn. 55404.

*Nospa (Chinoin, Budapest) isodihydropaperine hydrochloride.
†Segontin (Chinoin, Budapest) [N-3 phenyl-propyl-(2')]-1 1-diphenyl-propyl-(3)-amine. Identical preparation "Diphril" reproduced in Chemical-Pharmacol. Instit of Leningrad, USSR.
‡Ustimon (Oesterr Stickstoffwerke Austria, reproduced in Chemical-Pharmacol. Institut of Leningrad, USSR) 1,1'-[ethylenebis (methylimino)] dipropylbis (3 4,5-trimethoxybenzoate). Reproduced in Instit of Acad. Sci. Latvian, SSR.
§Intensain (Cassella-Riedel Pharma, Frankfurt West Germany) 3(β-Diethylamino-ethyl)-4-methyl-7 Carbethoxy-methoxy 2-oxo(1,2-chromen)-hydrochloride (reproduced Pliva, Yugoslavia).

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The arterial pulse in health and disease

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There is in clinical medicine no physical sign more basic or important than the arterial pulse. From ancient times the pulse has been recognized as the most fundamental sign of life. The early physicians (as we learn from the works of Galen[1]) paid great attention to the character of the pulse in health and the changes which occurred in disease. To the modern physician the pulse is beginning to assume even greater importance. The pulse reflects disease of the heart and arteries—from which most patients succumb. In attempting to follow changing cardiovascular status under emergency conditions the modern physician frequently records the pulse directly through an intra-arterial catheter and he wishes to gain as much information as possible from inspection of pulse contour Further he learns that the newer and most successful heart-assist devices have their desired effect on cardiac function by altering contour of the aortic pressure pulse, and he might wonder if subtle spontaneously occurring changes in pulse contour under disease conditions may adversely affect cardiac performance.

The modern physician who turns for guidance on the pulse and its interpretation t a cardiology textbook, to a medical text, or to a text on cardiac catheterization is likely to be confused misled and disappointed While importance of the pulse is undisputed and its increasing significance can hardly be denied It is almost incredible that text books have shown virtually no change in their descriptions and explanations of arterial pressure pulse contour over the last seventy years. When one compares the latest editions of the most authoritative American and English cardiology text books[2-4] with Broadbent's[5] and Mackenzie's[6] books on the pulse, published in 1890 and 1902 respectively (before introduction and clinical acceptance of the sphygmomanometer) one finds little advance of significance This failure of progress is hardly due to the field being fully and adequately covered at the turn of the century and is not due to lack of headway in subsequent years but rather is a consequence of the complicated nature of the subject and the inability of clinicians to absorb all the advances in hemodynamics that have been achieved by workers in the paramedical sciences.

This paper attempts a reassessment of the arterial pressure pulse in the light of advances which have been made since publication of Mackenzie's classic book It is proposed first to give an account of contemporary concepts of the arterial pulse as they appear in current cardiology textbooks and to point out some of the anomalies and

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myocardial capillaries by Intensain are not included in this study.[6] The results are summarized in two tables.

Table I shows the dosage mean latent period of therapeutic effect number of cases, side effects and mean change of frequency of angina attacks The initial frequency of attacks are similar for all six drugs indicating that the subgroups were reasonably well matched All drugs produced a significant decrease most pronounced with Segontin and Isoptin least pronounced with Papaverin All drugs were well tolerated by the large majority and side effects were few and mild While placebos were used the effect of Papaverin was utilized as statistical reference

For statistical comparison five criteria were used (1) per cent of favorable effects (2) per cent of patients with complete abolishment of anginal pain (3) per cent of patients with improvement of the ECG (resting or exercise) (4) per cent of patients for whom the given drug was most effective and (5) per cent of patients in whom the given preparation was the only effective one The results are shown in Table II

The differences in the per cent of favorable results except Papaverin with the lowest and Isoptin with the highest value ($p < 0.001$) are minor Regarding complete disappearance of pain and improvement of the ECG equally good results were obtained with Intensain Segontin and Isoptin The difference of the effect of Papaverin was significant ($p < 0.05$) The majority of patients responded favorably to most preparations used but with Isoptin and Segontin favorable effects were more frequent. Isoptin was also in 17.4 per cent, the only effective drug

However the authors emphasize that it is impossible to predict the most effective drug for a given patient, and that the choice is largely arbitrary Segontin and Isoptin were most effective for angina pectoris at rest as compared to the other preparations while Nospa was most effective for angina pectoris on emotional background

I am grateful to R. M Gabrielson, M D Warner Chilcott Laboratories, Morris Plains, N J for information about the drug compositions.

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Table I

Name	Derivation	Meaning
Anacrotic	Ana: up (Greek) Krotos: beat (Greek)	(1) A small slow-rising pulse with a notch on the ascending limb (2) Twice beating on the upstroke
Dicrotic	Di. twice (Greek) Krotos. beat (Greek)	One in which the dicrotic wave is exaggerated
Bisferiens	Bis: two (Latin) Feriens: to beat (Latin)	A pulse with two palpable peaks
W terhammer		The shock wave produced in a pipe when movement of fluid is suddenly stopped

and with mean arterial pressure (Fig 2) It is obvious that they represent different events and that each has a different sig nificance

Table I gives descriptions of different pulses as given in current medical dic tionaries together with their derivations. Many of these terms have been in use for centuries their origin is in most cases ob-scure although the term dicrotic can be traced back to Rufus of Ephesus in the first century A.D It will be noted that dicrotic and bisferiens" both mean literally "twice beating" with the first derived from Greek and the second from Latin In current usage the "dicrotic pulse has its second beat during diastole while the 'bisferiens pulse has its second beat during systole. The difference is not always clear although as described below the greatest confusion occurs between the bisferiens and the anacrotic" pulse.

Normality nd abnormality While ter minology is confused problems really begin when one attempts to identify what is artefact, to establish what is normal and to classify what is abnormal In contrast to the electrocardiogram (ECG) there are no accepted criteria of normality or ab-normality of the pulse and no set standards of performance for the manometers or sphygmographs used to record it. Mac kenzie[4] was more critical than many who have followed him about accuracy of the sphygmograph and attributed many of the features of his tracings to artefact. Sphygmographic tracings are frequently quite different to waves recorded directly in an artery under the tambour but it has not been established whether this is due to sphygmographic artefact or to longi tudinal movements of the artery such as those described by Anliker Moritz, and Ogden. Desired frequency response of manometers used to record human intra arterial pressure waves has been given by Patel and associates but it is extremely doubtful if these criteria are met in the tracings one sees in the textbooks or in many clinical journals. Very often it is not possible to be sure whether a given feature of a wave does in fact represent a true pressure fluctuation or whether it repre sents resonance of the catheter-manometer system. This is illustrated in Fig 4 which shows again the pulse wave recorded by Wiggers with a sensitive high frequency manometer and the same wave as it would have been recorded by an underdamped low-frequency manometer system similar to that frequently used in clinical diag nostic laboratories.

There is in the literature no agreement as to what is and what is not normal This is illustrated in Fig 5 which shows the aortic pulse of Wiggers taken from a normal dog and below an illustration from Wood s text which is said to demonstrate the anacrotic pulse of aortic stenosis. The waves are virtually identical yet these

An exception to this criticism is the latest (sixth) edition of Harrison Textbook of Internal Medicine

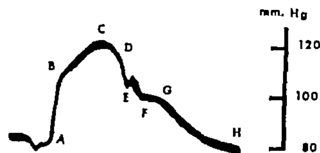


Fig 1 Central aortic pressure wave recorded in a normal dog (From Wiggers, C. J : Circulatory dynamics, New York, 1952, Grune & Stratton, Inc.)

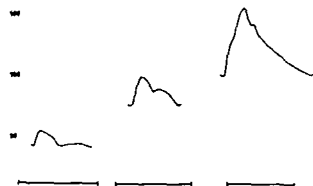


Fig. 2 Pressure waves in the ascending aorta of a rabbit under normal conditions (center) after injection of epinephrine (right) and after injection of pilocarpine (left) (From O Rourke M F Circ. Res. 27:11 1970, published by American Heart Association.)

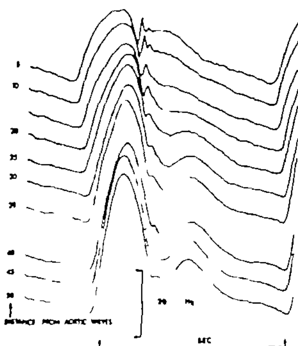


Fig 3 Pressure waves recorded at 5 cm. intervals between the aortic arch (above) and the iliac artery (below) in an Australian wombat. (From O Rourke, M F J Appl. Physiol 23:139 1967 published by American Physiological Society)

inconsistencies which exist. Next a brief resume will be given of the pulse as described by Mackenzie and his contemporaries. Then it is proposed to trace the advances in measurement and interpretation of the pulse that have been made over the last seventy years and finally to suggest how this information may be correlated to give a sensible description and rational explanation of the arterial pressure pulse as recorded directly under normal conditions and in a number of disease states

Descriptions of the pulse in modern clinical literature

Terminology Fig 1 shows a pressure wave recorded directly from the proximal aorta and published in Wiggers book Circulatory Dynamics. [7] In conventional clinical terminology[3-5] the first shoulder (*b*) is referred to as the percussion wave the second (*c*) as the tidal wave and the third (*g*) as the diastolic or dicrotic wave. This terminology is confusing because it is not consistent Percussion appears to refer to a mechanism diastolic describes timing in relation to the cardiac cycle while tidal has no clearly relevant meaning Dicrotic means literally twice-beating but in Fig 1 the dicrotic wave is actually the third undulation on the pulse Even the term diastolic is not always appropriate since the diastolic wave moves out of diastole into the systolic portion of the pulse when blood pressure rises (Fig 2)

The notch which separates the systolic from the diastolic part of the pressure wave is referred to as the incisura or dicrotic notch it is generally held that the two terms are interchangeable and that the notch is caused by aortic valve closure [1-4] However on close inspection of pressure waves such as the series in Fig 3 one finds that there are two notches, not one The first or true incisura is short and sharp most prominent in proximal vessels and is synchronous with aortic valve closure whereas the second—the true dicrotic notch—is more gentle most prominent in peripheral vessels and represents the foot of the diastolic wave Their relationship varies with site in the arterial tree (Fig 3)

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Waterhammer		The shock wave produced in pipe when movement of fluid is suddenly stopped

and with mean arterial pressure (Fig 2) It is obvious that they represent different events and that each has a different significance.

Table I gives descriptions of different pulses as given in current medical dictionaries together with their derivations. Many of these terms have been in use for centuries their origin is in most cases obscure although the term "dicrotic" can be traced back to Rufus of Ephesus in the first century A.D. It will be noted that "dicrotic" and "bisferiens" both mean literally "twice beating" with the first derived from Greek and the second from Latin. In current usage the "dicrotic" pulse has its second beat during diastole while the "bisferiens" pulse has its second beat during systole. The difference is not always clear although as described below the greatest confusion occurs between the bisferiens and the anacrotic pulse

Normality and abnormality While terminology is confused problems really begin when one attempts to identify what is artefact, to establish what is normal and to classify what is abnormal. In contrast to the electrocardiogram (ECG) there are no accepted criteria of normality or abnormality of the pulse and no set standards of performance for the manometers or sphygmographs used to record it. Mackenzie was more critical than many who have followed him about accuracy of the sphygmograph and attributed many of the features of his tracings to artefact. Sphygmographic tracings are frequently quite different to waves recorded directly in an artery under the tambour but it has not been established whether this is due to sphygmographic artefact or to longitudinal movements of the artery such as those described by Anliker Moritz, and Ogden.[8] Desired frequency response of manometers used to record human intra arterial pressure waves has been given by Patel and associates,[9] but it is extremely doubtful if these criteria are met in the tracings one sees in the textbooks or in many clinical journals. Very often it is not possible to be sure whether a given feature of a wave does in fact represent a true pressure fluctuation or whether it represents resonance of the catheter-manometer system This is illustrated in Fig 4 which shows again the pulse wave recorded by Wiggers with a sensitive high frequency manometer and the same wave as it would have been recorded by an underdamped low-frequency manometer system similar to that frequently used in clinical diagnostic laboratories.

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Fig 4 An aortic pressure pulse as recorded by an accurate sensitive manometer system (left) and as recorded by an underdamped manometer with low frequency response (right) For the latter pulse frequency taken as 90 beats per minute manometer natural frequency as 12 c.p.s. and damping coefficient as 0.16.

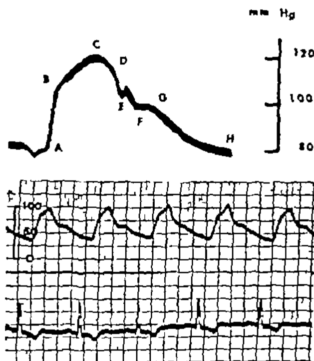


Fig 5 A normal aortic pressure pulse (top) (From Wiggers C. J Circulatory dynamics, New York 1952 Grune & Stratton, Inc.) The anacrotic pulse (bottom) of aortic stenosis. (From Wood P Diseases of the heart and circulation, London 1968, Eyre and Spottiswoode.)

authoritative texts by respected authors consider one to be normal and the other abnormal *Confusion is compounded when* one recalls from Fig 4 that a very common instrumental error can turn the same pulse into *a bisferiens contour*

Problems in classification of abnormal pulses have been recognized for many years. *Fig 6* shows Mackenzie s illustrations of an anacrotic pulse a bisferiens pulse and a normal pulse distorted by instrumental artefact There is only a minor difference between the anacrotic and bisferiens pulse an even greater difference was seen in the normal subject when the sphygmograph was underdamped According to Wood[3] anacrotic comes from *ana di crotic* and means literally twice beating on the upstroke By this terminology anacrotic and bisferiens should be synonymous. Most clinicians would I think *strenuously deny this*. Like Humpty Dumpty we each know what we mean by anacrotic and bisferiens but a glance at the literature shows *that we do not* all mean the same thing Wood s[3] illustration of a bisferiens pulse is very similar to the anacrotic pulse in the textbook of Hurst and Logue[9] The bisferiens pulse of Hurst and Logue is like Bramwell s waterhammer pulse.[10] Bramwell confuses matters further by showing on one page side by side two waves with virtually identical contour one of which is called normal and the other anacrotic, and another virtually identical pair one of which is called normal and the other waterhammer Confusion is compounded by the widespread use of *anacrotic pulse as being specific for aortic* stenosis and as describing a slow-rising pulse of low amplitude. Wood[3] points out that anacrotic makes no reference to amplitude and both Mackenzie[4] and Bramwell[10] described an anacrotic pulse with high pulse pressure in arteriosclerosis and hypertension as well as with low pulse pressure in aortic stenosis. Bramwell[10] showed that the anacrotic character of the pulse in aortic stenosis is dependent on heart rate and that the pulse reverts to a normal configuration when heart rate increases and stroke volume decreases.

At this time there is no less *confusion in classification of abnormal pulses than there was in the 1890 s when Broadbent*[11] and Steell[12] conducted a vigorous debate on the character of the pulse in aortic valve disease One might ask—how can we expect to advance in this field let alone communicate with each other and impart the art to our students when there is such confusion and uncertainty in the basic areas of accuracy in recording *identification of normal* limits and classification of abnormality If the years have a lesson to teach

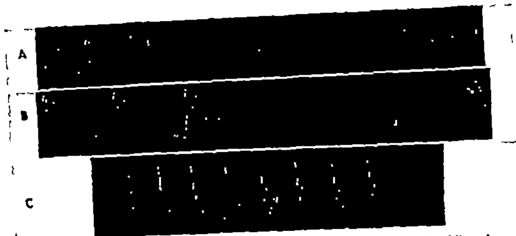


Fig. 6 Sphygmographic tracings showing an anacrotic pulse (*A*), "bisferiens" pulse (*B*) and normal pulse distorted by sphygmograph resonance (*C*). In the bottom panel is shown (dotted line) what Mackenzie considered to be the undistorted pulse contour. (From Mackenzie, J: The study of the pulse, arterial, venous, and hepatic and the movements of the heart, Edinburgh, 1902, Pentland.)

Table II. Explanations of features of the arterial pulse as given in standard cardiology texts by Wood,[3] *Friedberg, and Hurst and Logue*[5]

Percussion wave or anacrotic shoulder	Wood: "Shock of left ventricular contraction" Friedberg: "Shock transmitted by ventricular contraction" Hurst and Logue: "When the peak of ejection is maximal"
"Tidal" wave	Wood: — Friedberg: "Summation of the uncompleted percussion wave and waves reflected from the periphery" Hurst and Logue: "Continued but slower ventricular ejection in addition to reflected waves from the periphery"
Diastolic wave	Wood: "Shock of aortic valve closure" Friedberg: "Shock of closure of the aortic valve with consequent rebound of blood plus peripheral factors" Hurst and Logue: "Reflected waves from the periphery"

us, t is that ill-defined terms such as "bisferiens," anacrotic, and waterhammer are a barrier to understanding and progress.

Mechanisms. When one turns to mechanisms responsible for wave contour one finds that there is no consensus in the clinical literature on what is responsible for normal contour let alone contour of the wave under abnormal conditions. Most do agree that the percussion wave in an artery is due to arrival of the impulse generated by ventricular ejection but different explanations are given for the tidal and dicrotic waves (Table II). To be consistent these explanations must be compatible with explanations given for accentuation or disappearance of these waves under pathologic conditions. This is usually not the case. For example Wood[3] states with confidence and others agree[4] that an exaggerated diastolic wave—the dicrotic pulse—is a sign of peripheral vasodilation. There is no clear evidence that aortic valve closure is altered by vasodilation. Taking the alternative (and more likely) explanation for the diastolic wave, one would expect that vasodilation by decreasing the peripheral reflection coefficient would decrease, not increase, amplitude of the diastolic wave. Conversely one would expect vasoconstriction to cause exaggeration of the

diastolic wave When one looks for support for the textbook view one finds it lacking and one finds the idea that a dicrotic pulse is a sign of peripheral vasodilation has developed over the years, and like the story of Dr Uplavici [12] has been handed down without proof or challenge

There are some curious and erroneous statements in the clinical texts on explanations of wave contour The most common relates to the lowest point on the wave—the diastolic blood pressure Many consider peripheral resistance to be *uniquely related* to diastolic pressure rather than to mean arterial pressure Pickering[14] and Dexter[15] point out that peripheral resistance is related through cardiac output to mean arterial pressure and that systolic and diastolic pressures represent simply the highest and lowest points of the oscillation around this mean Yet Wood[3] goes so far as to state that conditions characterized by a low diastolic pressure including aortic *incompetence and heart block* (and sometimes arteriosclerosis) are associated with peripheral vasodilation Hurst and Logue[3] likewise explain the collapsing pulse in aortic incompetence to be due largely to peripheral vasodilation rather than entirely due to valvular *regurgitation* The supposed vasodilation in heart block and in aortic incompetence has never been documented and doubtless does not occur There is no need whatever to invoke vasodilation *to explain a low diastolic pressure* or a rapid fall in pressure from a high *systolic peak*

Descriptions of the pulse in older literature

In a sense the clinicians of the 1890 s were more careful in their descriptions of the pulse than are their modern counterparts. This was largely a *matter of necessity* before introduction of the sphygmomanometer it was necessary to diagnose hypertension and hypotension from palpation of the pulse All terminology now used was current at that time embellished by other descriptions *such as pulsus myurus* (the mousetail pulse) *and pulsus formicans* (a small feeble pulse likened to the movement of ants)

Mackenzie[4] was one of the *first to* record the pulse with a sphygmograph He noted that anacrotic bisferiens and dicrotic *pulses could be recorded from normal individuals*. He was very aware of instrumental artefact in his tracings and emphasized the care needed to distinguish the subtle difference between a bisferiens and an anacrotic pulse Mackenzie interpreted anacrotic literally as meaning a pulse with a shoulder or small wave on its upstroke and described it at least as often in patients with arteriosclerosis as in patients with aortic stenosis Prior to Mackenzie a great deal of confusion in terminology had arisen from Broadbent s[11] and Steell s[12] interpretations of the bisferiens and anacrotic pulses in aortic valve disease To the latter the two pulses were quite different whereas to the former they were apparently almost identical

Following Mackenzie there was for many years less semantic debate about arterial pulse contour Lewis[16] in his textbook did not mention the terms anacrotic or bisferiens and neither did Osler [17] Osler did however refer to the dicrotic and water hammer pulses, and these terms were also used later by Evans.[18] Osler pointed out that a dicrotic pulse is often seen in typhoid fever associated with toxemia Mackenzie[4] stated that in fevers softening of the pulse with increasing dicrotism is the symptom of increasing exhaustion Neither of these great teachers *inferred that* a prominent diastolic wave is a sign of vaso*dilation*

It is difficult to find the basis of the currently held view that a dicrotic pulse indicates peripheral vasodilation Frank (quoted by Kroeker and Wood[19]) described in the early part of this century a dicrotic pulse in patients with fevers and in others *after inhalation of amyl nitrite. He at*tributed the phenomenon not to vasodilation but to the accompanying shortening of ventricular ejection period

It is not difficult to support the argument that the clinical literature has shown little improvement in description or interpretation of arterial pulse *contour* since the early 1900 s. The position at that time was summarized by Mackenzie[4] I think it will be readily admitted by all who are familiar with books dealing with the pulse that the present day knowledge is not only imperfect—it is chaotic.

Advances in arterial hemodynamics

Measurement All the records published by Broadbent, Steell, and Mackenzie were taken with a sphygmograph with the use of a rather crude tambour applied to the skin overlying an artery High fidelity manometers were introduced by Frank[20] and subsequently refined by Wiggers[21] Hamilton[22] Lilly[23] and others, and used in man by Cournand and Ranges.[24] Methods for accurately recording phasic flow came later the electromagnetic blood flowmeter (now generally regarded as the standard of reference) was introduced independently by Kolin[25] and Wetterer[26] in 1936 and 1937 These instruments have been used for recording pulsatile flow in humans over the past fifteen years.[27-29] Accurate techniques for measuring arterial diameter have recently been introduced.[30-32] These have disproved Mackenzie's contention that the arterial pulse one feels is due to longitudinal movement of the artery and have shown that pulsatile changes in diameter are virtually identical to the pressure pulse (the minor differences between pressure and diameter waves being readily explained in terms of nonlinear elasticity and viscosity of the arterial wall)

Analysis of wave contour With these methods of measuring pressure flow and diameter a great deal of data has been obtained from experimental animals and from humans. The earliest and most obvious approach to analysis of this data was through consideration of wave contour The major contribution in this field was the classic paper of Hamilton and Dow[33] published in 1939

Hamilton and Dow recorded pressure waves at intervals between the ascending aorta and femoral artery of dogs. They explained pressure wave contour in different vessels in terms of wave reflection between the aortic valves and peripheral sites. They likened the arterial system to a tube or organ pipe with two closed ends, one representing the aortic valves and the other the resultant of all peripheral reflecting sites. They considered that the arterial pulse bounced back and forth between these sites, setting up a system of standing waves in the aorta.

This simple schematic model was not improved by further attempts at sophistication with the use of the same method of analysis. Many subsequent workers either accepted the model too literally (and began searching for a point in the aorta from which the wave was reflected debating whether this site behaved as an open or closed end) or did not accept it at all. Monumental attempts to explain arterial properties through consideration of wave shape only[34,35] appear to have confused rather than clarified the position. The fundamental deficiency in this approach to analysis and interpretation is that it is qualitative or at best semiquantitative, and one needs more precise information than this to define arterial properties.

A number of criticisms arose to the standing wave hypothesis. First, not all would agree with Hamilton and Dow[33] that their findings were regularly seen in dogs, and even these authors acknowledged that many other species, including man did not show the exact changes in the aortic pulse that they had observed in dogs. Further it was pointed out that standing waves could occur only if there were no attenuation of the wave in travel if there were complete reflection of the wave and if there were no interaction of reflected waves from scattered arterial terminations. The main criticism of the Hamilton and Dow hypothesis came from McDonald and Taylor[36,37] who used a different approach to analyze the pulse and who considered that wave reflection was too low and attenuation too high for resonance and standing waves to occur As so often happens, subsequent events suggest that the truth probably lies somewhere between the differing views of these two schools.[38,39]

The most precise information about functions of the arterial system has come from quantitative studies of the arterial pulse The most popular method is analysis of the frequency components of the pulse. For a number of reasons this will be discussed in some detail. First, in recent years analysis of the frequency components of the pulse appears to have given more information on arterial properties than any other approach. Second this type of analysis is not well described in clinical literature and is not readily understood by clinicians. The third reason is that at least

diastolic wave. When one looks for support for the textbook view one finds it lacking and one finds the idea that a dicrotic pulse is a sign of peripheral vasodilation has developed over the years and, like the story of "Dr Uplavici",[12] has been handed down without proof or challenge.

There are some curious and erroneous statements in the clinical texts on explanations of wave contour. The most common relates to the lowest point on the wave—the diastolic blood pressure. Many consider peripheral resistance to be uniquely related to diastolic pressure rather than to mean arterial pressure. Pickering[13] and Dexter[15] point out that peripheral resistance is related through cardiac output to mean arterial pressure and that systolic and diastolic pressures represent simply the highest and lowest points of the oscillation around this mean. Yet Wood[3] goes so far as to state that conditions characterized by a low diastolic pressure including aortic incompetence and heart block (and sometimes arteriosclerosis) are associated with peripheral vasodilation. Hurst and Logue[4] likewise explain the collapsing pulse in aortic incompetence to be due largely to peripheral vasodilation rather than entirely due to valvular regurgitation. The supposed vasodilation in heart block and in aortic incompetence has never been documented and doubtless does not occur. There is no need whatever to invoke vasodilation to explain a low diastolic pressure or a rapid fall in pressure from a high systolic peak.

Descriptions of the pulse in older literature

In a sense the clinicians of the 1890's were more careful in their descriptions of the pulse than are their modern counterparts. This was largely a matter of necessity: before introduction of the sphygmomanometer it was necessary to diagnose hypertension and hypotension from palpation of the pulse. All terminology now used was current at that time embellished by other descriptions such as *pulsus myurus* (the mousetail pulse) and *pulsus formicans* (a small feeble pulse likened to the movement of ants).

Mackenzie[6] was one of the first to record the pulse with a sphygmograph. He noted that anacrotic, *bisferiens*, and dicrotic pulses could be recorded from normal individuals. He was very aware of instrumental artefact in his tracings and emphasized the care needed to distinguish the subtle difference between a bisferiens and an anacrotic pulse. Mackenzie interpreted "anacrotic" literally as meaning a pulse with a shoulder or small wave on its upstroke and described it at least as often in patients with arteriosclerosis as in patients with aortic stenosis. Prior to Mackenzie a great deal of confusion in terminology had arisen from Broadbent's[11] and Steell's[12] interpretations of the *bisferiens* and anacrotic pulses in aortic valve disease. To the latter the two pulses were quite different, whereas to the former they were apparently almost identical.

Following Mackenzie there was for many years less semantic debate about arterial pulse contour. Lewis[16] in his textbook did not mention the terms anacrotic or bisferiens and neither did Osler.[17] Osler did however refer to the dicrotic and water-hammer pulses and these terms were also used later by Evans.[18] Osler pointed out that a dicrotic pulse is often seen in typhoid fever associated with toxemia. Mackenzie[6] stated that in fevers "softening of the pulse with increasing dicrotism is the symptom of increasing exhaustion." Neither of these great teachers inferred that a prominent diastolic wave is a sign of vasodilation.

It is difficult to find the basis of the currently held view that a dicrotic pulse indicates peripheral vasodilation. Frank (quoted by Kroeker and Wood[19]) described in the early part of this century a dicrotic pulse in patients with fevers and in others after inhalation of amyl nitrite. He attributed the phenomenon not to vasodilation but to the accompanying shortening of ventricular ejection period.

It is not difficult to support the argument that the clinical literature has shown little improvement in description or interpretation of arterial pulse contour since the early 1900's. The position at that time was summarized by Mackenzie:[6] "I think it will be readily admitted by all who are familiar with books dealing with the pulse that the present day knowledge is not only imperfect—it is chaotic."

this way one can dismiss the method as useless if another pair of waves recorded in the same artery under the same conditions gives different values of impedance. In other words, if vascular impedance is to have any meaning there must be a linear relationship between pressure and flow. The first harmonic of pressure must be related exclusively to the first harmonic of flow and to no other flow harmonic; there must be no harmonic interaction. Proof that harmonic interaction is extremely small comes from a number of sources[illegible] and Fig. 9 shows one of the pieces of evidence. This figure shows impedance in the femoral artery of a dog obtained from pressure and flow waves which were recorded with the heart beating irregularly. Despite great variations in amplitude of pressure and flow harmonics and despite the fact that impedance values at similar frequencies were determined from different harmonics of long and short waves, all values fell along the same regular curve. It is generally conceded at this time that for practical purposes under most conditions there is a linear relationship between pressure and flow at the same point in an artery and between pressure and pressure at different points in the arterial system.

Frequency analysis thus enables us to describe a wave in precise mathematical terms and to define the relationship between different waves. Indeed one can go further. Just as one can infer the resistive properties of the peripheral vasculature from calculated resistance, one can interpret from impedance curves the factors responsible for the relationship between pulsatile pressure and flow. The concept of input vascular impedance was introduced by Taylor and he is also responsible for interpretation of impedance curves in terms of vascular properties. His works and those of his mentor McDonald may be consulted for details.[illegible]

From the relationship of resistance to the minimal and subsequent values of impedance modulus in Fig. 9, one can deduce that the coefficient of reflection in peripheral vessels is approximately 0.8. In other words, the wave reflected from the peripheral bed has an amplitude which is 80 per cent of the incident wave. The pressure wave recorded in the femoral artery is the

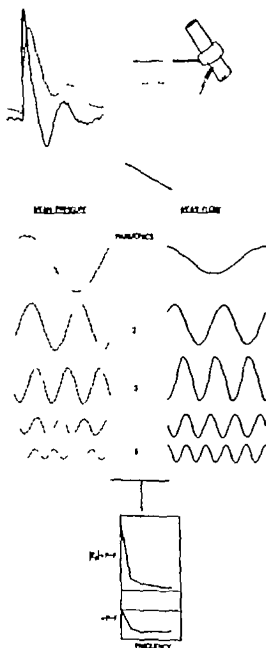


Fig. 8. Stages in the determination of vascular impedance. Pressure (dotted line) and flow (solid line) waves recorded simultaneously in an artery are each broken down into mean values and a series of harmonic sine waves. The corresponding terms of pressure and flow are related to give modulus (Z_o) and phase (ϕ) of impedance. (From O'Rourke, M. F., and Taylor, M. G.: Circ. Res. 18:126, 1966, published by American Heart Association.)

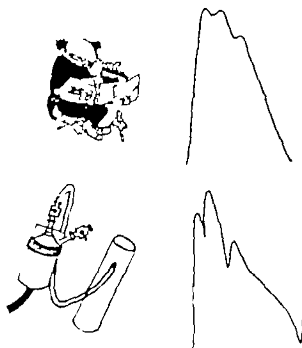


Fig 7 The musical note from a flute (top) frequency 256 c.p.s. and an arterial pressure pulse (bottom) frequency 1 c.p.s. Flautist from *The Hoffnung Symphony Orchestra* by Gerald Hoffnung published by Dobson Books London.

one report in an authoritative clinical journal has underplayed its significance and importance [40]

Frequency analysis of the pulse The conventional approach to analysis of the pulse suffers from the disadvantage of being only descriptive and qualitative While it is perfectly acceptable to describe a phenomenon such as the pulse in terms of its easily identifiable features this approach is quite restrictive when one wants to convey information accurately to others when one wants to describe features that are not easily identifiable or which are mixed with or obscured by other features or when one wants to investigate underlying mechanisms.

An alternative approach (which has the advantage of being strictly quantitative) is to consider the pulse as a series of frequency components. This approach is quite familiar in analysis of musical waves We refer quite easily to the musical note in Fig 7 in terms of its harmonic components. It is equally acceptable to consider a pressure or flow wave which is regularly repeated as a series of harmonics. While used to a limited degree in earlier years, this method was firmly established in 1955 by McDonald and Womersley[41 42] and has been used extensively by others since Frequency analysis has long been a standard procedure in the physical sciences and is used widely in electrical and acoustic engineering and in other fields.

Fig 8 shows pressure and flow waves recorded simultaneously in an artery broken down into their mean values and first five harmonics. Each harmonic component has a definite modulus or amplitude and a definite phase or delay from a set point of reference Given modulus and phase of the different harmonics of the pulse one can resynthesize the original wave. Thus the first advantage of harmonic analysis is that it enables one to describe the arterial pulse in quantitative terms. But this is just the beginning The principal value of the analysis stems from the fact that one can compare corresponding components of waves recorded simultaneously Fig 8 is an example This shows pressure and flow waves recorded simultaneously in the femoral artery of a dog From inspection of wave contour one gains little information on the relationship between the waves or of the properties of the vascular system which determine this relationship By measuring and relating mean values of the waves one can calculate vascular resistance and interpret from this the resistive properties of the vessels downstream In precisely the same way one can compare corresponding frequency components of pressure and flow—the first harmonic of pressure with the first harmonic of flow the second harmonic of pressure with the second of flow and so on The results one obtains are of vascular impedance the relationship of pressure to flow at frequencies which are multiples of heart rate Such a graph is shown at the bottom of Fig 8 Impedance is a complex quantity and has two components modulus and phase lag At any frequency modulus is the ratio of the moduli or amplitudes of corresponding pressure and flow harmonics. Phase lag is the delay between corresponding pressure and flow harmonics. Negative phase lag indicates that flow preceeds pressure

While there can be no argument about describing pressure/flow relationships in

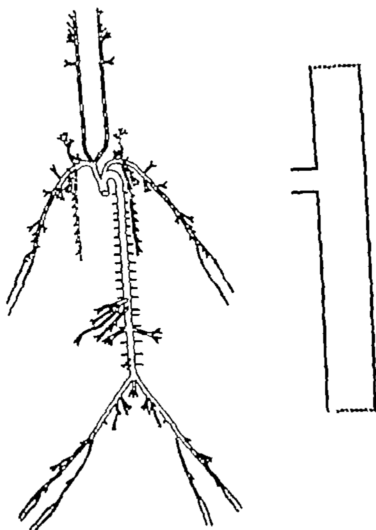


Fig. 10. A model of the systemic arterial system. For explanation see text. (From O'Rourke, M. F.: J. Appl. Physiol. 23:139, 1967, published by American Physiological Society.)

8/10 of the low frequency components of the incident wave. The end of the tube represents the resultant of many individual reflecting sites, each being a point in the vascular bed where a high resistance arteriole arises from a low resistance artery.[33,44]

Particularly interesting results have come from interpretation of impedance curves from the ascending aorta and major central arteries. Impedance determinations from vessels supplying the upper (brachiocephalic and left subclavian arteries) and lower (descending thoracic aorta) parts of the body indicate the presence of a single functionally discrete reflecting site in the vascular bed beyond. In the ascending aorta, however, impedance determinations show evidence of two functionally discrete reflecting sites at different distances from the heart. It has been suggested that these two sites represent the lumped vascular beds of the upper and lower parts of the body in parallel.[44] Thus impedance determinations suggest that the whole systemic circulation may be represented by a simple asymetric T-tube model (Fig. 10): the shorter arm represents all arteries in the head, neck, and upper limbs; the longer arm represents the descending aorta and all arteries in the trunk and lower limbs; the upper end represents all arterioles in

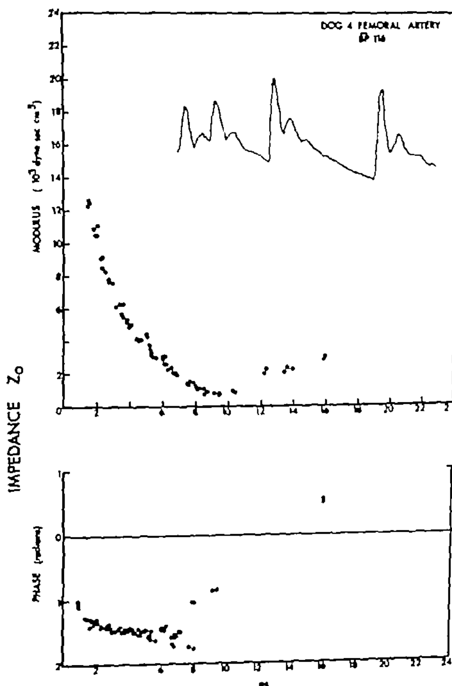


Fig 9 Vascular impedance under control conditions in the femoral artery of a dog Impedance was determined from a series of 11 pairs of waves recorded during marked sinus arrhythmia. Abscissa cycles per second (From O'Rourke M F and Taylor M G. Circ. Res. 18:126, 1966, published by American Heart Association.)

summation of incident and reflected waves. Studies of vascular impedance show that intra arterial injection of a vasodilator drug causes reduction in reflection coefficient almost to zero while injection of a constrictor causes increase in reflection coefficient almost to unity [44] Besides giving information on magnitude of reflection impedance curves give the actual position of the resultant of all individual reflecting sites in the vascular bed In Fig 9 the numerical values of impedance modulus and phase are minimal at 10 c.p.s. Assuming a wave velocity of 10 M per second in arteries of the leg the reflection site is calculated to be one quarter wavelength or (10 + 10)/4 = 25 cm distal to the recording site in the femoral artery In this dog the site corresponded to a point just below the knee.

Impedance graphs such as the one in Fig 9 suggest that the femoral vascular bed behaves like a single tube terminating in a resistance which causes reflection of

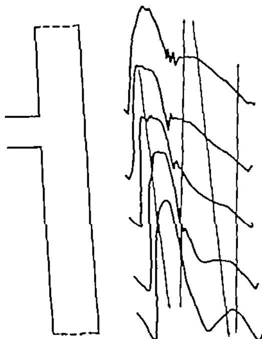


Fig. 13 Formation of normal aortic pressure pulses. For explanation see text.

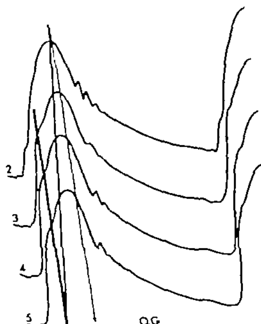


Fig. 14 Pressure waves recorded in the aortic arch, iliac artery and intermediate sites of patient with arteriosclerosis. Heart rate, 60 beats per minute; measured pulse wave velocity 12.5 M per second. Lines drawn to show passage and repassage of the impulse over the arterial system at this velocity.

the reflected wave returning from the lower part of the body. Likewise, (though in the interests of simplicity it is not indicated in Fig. 13) it can be shown that the earlier tidal wave in the proximal aortic pulse is due to wave reflection in the upper part of the body. Thus we can say with some confidence that in the normal proximal aortic pulse the percussion wave is due to arrival of the impulse generated by ventricular ejection, the tidal wave is its echo from the upper part of the body, and the dicrotic or diastolic wave is its echo from the lower part of the body. Contour of the pulse in peripheral arteries can be explained in similar terms, bearing in mind altered time relationships of incident and reflected waves at different distances from the peripheral reflecting sites.

Explanation of pulse contour under abnormal conditions

HYPERTENSION AND ARTERIOSCLEROSIS. In hypertension[22] and arteriosclerosis[23] amplitude of the aortic pressure pulse is increased, the tidal wave is prominent, and the diastolic wave is absent. In these conditions pulse wave velocity is increased[24] so that the wave traverses the arterial system more quickly. All features of the pulse can be explained on the basis of increased wave velocity (Fig. 14). The wave reflected from the lower part of the body returns to the proximal aorta not during diastole but during the later part of systole where it merges with the echo from the upper-body reflecting sites to augment the tidal wave and increase systolic pressure. These changes in wave contour can be seen to develop and regress during and after intravenous infusion of a drug which increases mean arterial pressure.

In hypertension and arteriosclerosis there is less evidence of reflected waves as discrete components of the arterial pulse than under normal conditions. Such is the case even when hypertension is caused by increase in peripheral resistance, i.e., when the peripheral-reflection coefficient is increased. This paradoxical finding is readily explained when one considers that the pressure wave is more widely spread over the arterial system at any one point in time when wave velocity is high than when it is lower. Under these conditions incident, reflected and rereflected waves are blended and not recognizable as discrete events.

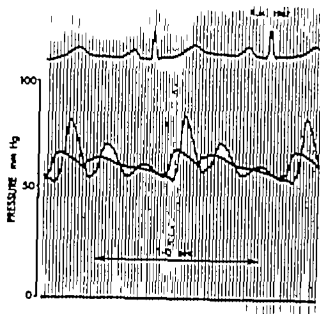


Fig. 11 Pressure waves recorded simultaneously in the aortic arch and brachial artery of a 55-year-old man with hypotension and clinical features of peripheral vasoconstriction. Damped natural frequency of both manometer systems exceeded 20 c.p.s. (From O Rourke M F Cardiovasc. Res. 4:291 1970, published by British Medical Association.)

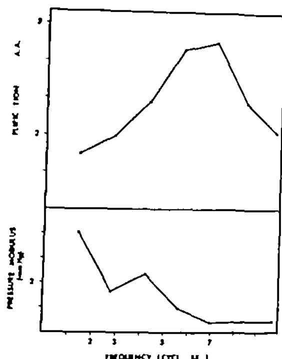


Fig. 12 Ratio of corresponding harmonics of the brachial and aortic pressure waves shown in Fig. 11 (top). Modulus of harmonics of aortic pressure waves in Fig. 11 (bottom). (From O Rourke, M F Cardiovasc. Res. 4:291 1970 published by British Medical Association.)

the upper part of the body and the lower end represents all arterioles in the lower part of the body

Beside explaining impedance curves this model is better able to account for patterns of pressure and flow in major arteries than is the model of Hamilton and Dow[33] and the earlier model of McDonald and Taylor[34,37] The model differs from that originally suggested by Hamilton and Dow in that it has a more realistic peripheral reflection coefficient and in that it down plays the role of wave reflection at the aortic valve while stressing the importance of wave reflection at the two lumped arteriolar reflecting sites in the upper and lower parts of the body This model based on relatively precise information on location and intensity of peripheral reflection enables simple and logical explanations to be offered for many of the features of arterial pressure and flow waves recorded in humans under different conditions.

Frequency analysis also assists in interpretation of pressure wave transmission in a vascular bed[34,37] This is illustrated in Figs. 11 and 12 Fig 11 shows pressure waves recorded simultaneously in the aortic arch and brachial artery of a patient with hypotension and signs of marked peripheral vasoconstriction Fig 12 gives results of analysis of the frequency components of these waves From these results one can infer that the unusual features of the aortic and brachial pulses were due to a combination of short sharp ventricular ejection low wave velocity and peripheral vasoconstriction[41]

Interpretation of the arterial pulse

Explanation of normal pulse contour The model suggested by impedance studies helps explain contour of the pulse in major arteries. Fig 13 shows pressure waves recorded between the brachiocephalic and femoral arteries of a dog set against corresponding parts of the model A line has been drawn to show passage of the original impulse generated by ventricular ejection back and forth between upper and lower body reflecting sites at a speed of 6 M per second—that is at the velocity of the foot of the pulse It can readily be seen that summation of incident and reflected waves is responsible both for amplification of the pulse in peripheral arteries and for the dicrotic or diastolic wave. In the proximal aorta the diastolic wave is clearly due to

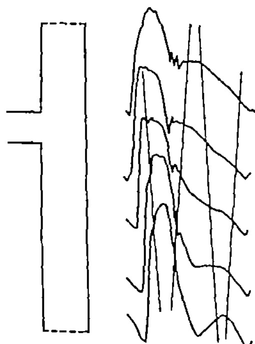


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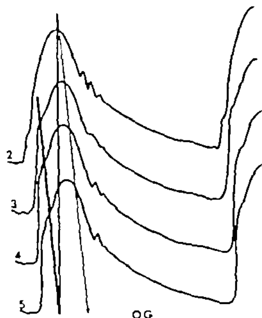


Fig. 14 Pressure waves recorded in the aortic arch iliac artery and intermediate sites of a patient with arteriosclerosis. Heart rate, 60 beats per minute measured pulse wave velocity 12.5 M. per second. Lines drawn to show passage and repassage of the impulse over the arterial system at this velocity

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When as in arteriosclerosis and hyper tension arterial pulse wave velocity is high the central aortic and peripheral arterial pressure pulses are more similar in amplitude and contour than under normal conditions. This again is a consequence of high wave velocity in central vessels there is less delay between incident and reflected waves so that the summation effect is nearly as great as at the periphery

It is interesting to note that before introduction of the sphygmomanometer hypertension was diagnosed on the basis of a peripheral pulse like those in Figs 2 and 14 i e a pulse in which the amplitude fell smoothly during diastole from a prominent systolic peak and which was associated with continued palpability of the artery throughout diastole [6]

AORTIC COARCTATION In aortic coarctation the normally placed lower body reflecting site is replaced by another much closer to the heart The pressure wave traverses the arterial system more quickly because of its smaller dimensions as well as its increased distending pressure Central aortic pressure waves in coarctation are similar to those seen in arteriosclerosis and severe hypertension and quite different from those normally seen in children and young adults.[42 44]

HYPOTENSION Pulse wave velocity is decreased in hypotension the impulse traverses the arterial system more slowly so that in the aortic pulse the tidal and diastolic waves are further displaced from the percussion wave (Fig 2) The tidal wave is frequently less obvious than usual because it occurs so late in systole when pressure is falling steeply On the other hand the diastolic wave is frequently more obvious than usual This can be attributed to the fact that with slow wave velocity the disturbance generated by ventricular ejection is at any time more discretely localized in space—and so at any one site more discretely localized in time. This tendency for the diastolic wave to be exaggerated in hypotension is potentiated by shortening of the ejection period[19] and by vasoconstriction [31] The most prominent diastolic waves are seen when all three factors are combined (Fig 11)

AORTIC VALVE DISEASE. The characteristic pressure pulse of aortic stenosis can be attributed to two factors of which prolongation of ventricular ejection is probably less important and Venturi effects in the aorta more important The hemodynamic situation in aortic stenosis may be mimicked in animals by compressing the ascending aorta with an unduly tight electromagnetic flow transducer [34] Under these circumstances it is found that the slow rise in aortic pressure the late systolic peak, and the low amplitude of the pulse distal to the probe can be attributed to the relative decrease in lateral pressure within the high velocity jet issuing from the constriction

A similar situation occurs when stenosis is combined with incompetence of the aortic valve Here pulse pressure is normal or increased but the upstroke is interrupted by a notch which is most prominent at the instant of peak ventricular ejection [33] Thus the same mechanism is involved in genesis of the anacrotic pulse of aortic stenosis and the bisferiens pulse of combined stenosis and incompetence There is no fundamental difference between the two they reflect the same process and a continuous gradation is seen between one and the other

IDIOPATHIC HYPERTROPHIC SUBAORTIC STENOSIS (I H.S S) A twice-beating pulse is frequently encountered in this condition as in combined aortic stenosis and incompetence. The underlying mechanism however is probably quite different because in I H.S.S the aortic flow wave has a biphasic contour[37 38] with systole divided into an early phase of rapid ventricular ejection and a later phase of reduced but sustained flow velocity The bisferiens contour of the pulse in I H.S.S is probably due to the unusual pattern of ventricular ejection

Terminology

There is much to be said for attempting to rationalize the nomenclature applied to the arterial pulse. With respect to normal pulse contour it would seem best to discard percussion tidal and dicrotic waves and introduce a system which refers entirely to timing or entirely to mechanism For the former one may substitute early systolic, late systolic, and diastolic for percussion tidal and dicrotic, and for the latter impact cephalic

reflected and caudal reflected. The former system (with nomenclature based on timing) appears simpler and better.

Perhaps the more familiar terms "anacrotic," "bisferiens," "dicrotic," and "waterhammer" should go the same way as "myurus" and "formicans"—out. To be useful these terms should aid description and assist in communication. There is much evidence that they do neither. Further, preoccupation with classification of the pulse into one or another category may distract attention from other more important considerations. Further still, as Mackenzie stressed, classification of the pulse does not necessarily help separate normality from abnormality nor distinguish between different types of abnormality. These names are little better than Galen's complicated and confusing descriptions which, as Broadbent[1] discussed, retarded medical progress for centuries. The best and most eloquent descriptions of the pulse are clear and concise, as Corrigan's[44] description of the pulse in aortic incompetence. It is suggested that instead of a blanket classification the pulse be described in simple terms, i.e., instead of an "anacrotic" pulse in aortic stenosis, a pulse with slow rise and low amplitude in aortic stenosis, instead of a "bisferiens" pulse, a pulse with two systolic peaks, and so on.

However desirable such a system may be for describing the pulse felt at the bedside, it is infinitely better for describing the recorded intra-arterial pulse. When striving for precision and accuracy by recording the pulse directly, it is most inappropriate to restrict oneself to terminology developed for another purpose in another age. One is likely to gain more information from a precise and clear description of the pulse and sometimes even more still from consideration of its frequency components.

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Appraisal and reappraisal of cardiac therapy

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Bretylium tosylate

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Bretylium tosylate, a benzyl quaternary ammonium compound, has recently been recommended, with extensive experimental and limited clinical support, as an important agent in the therapy and prevention of cardiac arrhythmias, especially recurrent ventricular tachycardia and fibrillation. The precise role of bretylium has not been determined. In this review the available information will be summarized with an attempt to place current knowledge of bretylium in perspective, as there is divergent opinion as to its value, proper dosage, and toxicity.

Pharmacology

Bretylium was initially used as an antihypertensive agent because of its ability to block postganglionic sympathetic nerve transmission. The drug selectively accumulates in sympathetic ganglia and their postganglionic nerves; this selective accumulation probably inhibits transmitter release by depressing adrenergic nerve terminal excitability. Although a number of studies of the effects of bretylium are available, the mechanisms of its blocking actions remain unclear. Catecholamine stores are not depleted, but a brief sympathomimetic effect occurs due to catecholamine release from sites peripheral to the adrenergic nerve blockade. The effects of bretylium resemble those of guanethidine and surgical sympathectomy, including a marked sensitivity to catecholamines. Bretylium is not metabolized but is excreted unchanged in the urine; its effects last approximately 6 to 8 hours. It is rapidly absorbed from intramuscular sites, but when administered orally only 15 to 20 per cent is absorbed from the gastrointestinal tract. The drug was abandoned as an oral antihypertensive agent because of the erratic and poor oral absorption, rapidly developing tolerance, and troublesome side effects, particularly postural hypotension.

Physiologic studies following parenteral bretylium indicate that doses of 2.5 to 10 mg. per kilogram increase myocardial contractility and occasionally blood pressure, for brief periods of three to twenty minutes. These effects are probably due to release of myocardial and adrenal catecholamines. Cardiac sympathetic nerve stimulation following bretylium neither increases myocardial contractility nor releases cat

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echolamines. Bretylium blocks the cold pressor response, increases blood flow to the extremities, and may block coronary artery vasoconstriction. Following bretylium, catecholamine effects on the myocardium and peripheral vascular resistance are enhanced and prolonged. Hemodynamic studies by Taylor and Donald[7] of normal subjects and patients with rheumatic heart disease or hypertension demonstrated that bretylium caused occasional profound hypotension following intravenous doses of 40 to 600 mg, although usually the blood pressure fall was proportional to dosage. Bretylium slightly increased resting cardiac output and oxygen consumption without changing the cardiac output response to exercise. Systemic blood pressure fell with exercise, returning rapidly to pre-exercise levels. In the normal and hypertensive patients the drug caused a rise in pulmonary arterial resistance and a fall in pulmonary wedge pressure. The effect on these parameters in the patients with rheumatic heart disease was variable.

In anesthetized dogs following ligation of the anterior descending coronary artery, locally infiltrated procaine or systemic bretylium appeared to protect against myocardial infarction. This protection presumably results from inhibition of reflex vasospasm. On the other hand, there are indications that agents which increase myocardial contractility, including bretylium, may be deleterious when treating subjects with acute myocardial injury, as myocardial O_2 consumption requirements increase with no improvement in cardiac function.

The antiarrhythmic potential of bretylium was first evaluated in 1965 by Leveque.[2] Bretylium prevented atrial fibrillation in dogs; its effectiveness varied with dosage in ranges of 2.5 to 30 mg. per kilogram. The maximum drug effect appeared approximately four hours after administration and was greatly diminished by eight hours. Studies by Bacaner[3-4] of bretylium's effect on the fibrillatory threshold of canine hearts to electric fibrillation indicated that 5 mg. per kilogram of the drug raised the fibrillatory threshold 2½ to 3 times that of the control state. Protection against ventricular fibrillation appeared twenty to thirty minutes after drug administration and the effectiveness increased over the ensuing two to three hours. Similar studies with lidocaine, procainamide, quinidine, diphenylhydantoin, guanethidine, and propranolol indicated that only propranolol had similar antifibrillatory effects. Lidocaine, procainamide, propranolol, and low dose diphenylhydantoin (4 mg. per kilogram) did not seem to block the antiventricular fibrillatory effects of bretylium. Diphenylhydantoin in high doses (10 to 50 mg. per kilogram), quinidine, and guanethidine either blocked or partially blocked the protective effect of bretylium. In addition to prevention of electrically induced ventricular fibrillation following bretylium, the ventricular fibrillation often reverted to sinus rhythm after periods up to 70 seconds. This phenomenon did not occur in untreated dogs. Bretylium also prevented hypothermia-induced ventricular fibrillation in experimental animals. In other studies, it was found that ventricular tachycardia and supraventricular tachycardia, induced in anesthetized dogs by epinephrine or ouabain, could be reversed with bretylium in doses of 15 to 20 mg. per kilogram.

Electrophysiologic studies of bretylium in rabbit atria showed that therapeutic concentrations did not affect action potential height, rate of phase four rise, or conduction velocity. When placed on the sciatic nerve, bretylium was 90 times less potent than procaine and 300 times less active than propranolol as a local anesthetic. Bigger and Jaffe[4] studied the electrophysiologic effects of bretylium on dog heart papillary muscle and Purkinje fibers. In therapeutic concentrations, bretylium did not affect phase four depolarization, automaticity, or the relationship between effective refractory period and action potential duration. Both of the latter were prolonged without slowing conduction. The authors point out that these effects are quite different from all other antiarrhythmic agents (quinidine, procainamide, diphenylhydantoin, propranolol, and lidocaine) which depress automaticity in Purkinje fibers and lengthen the effective refractory period relative to action potential duration. The antiarrhythmic effects of bretylium were not adequately explained by the effects on electrophysiologic properties of the Purkinje and ventricular muscle fiber cell membranes. The authors suggest that bre-

tylium may be effective primarily through its adrenergic blocking action. The slight rise noted in resting transmembrane voltage and V_{max} was thought possibly secondary to the initial bretylium effect of releasing catecholamines, since catecholamines are known to produce such effects. The sole direct effect of bretylium was prolongation of the action potential and lengthening of the effective refractory period without slowing conduction. Such effects might abolish re-entrant arrhythmias.

Clinical studies

A number of studies have been initiated to evaluate the role of bretylium in treating patients with cardiac arrhythmias. Bacaner administered bretylium (5 mg. per kilogram) to 35 consecutive cardiac surgical patients and compared the results with a control group of 38 patients. When arrhythmias occurred postoperatively, bretylium was repeated in a dosage of 5 to 8 mg. per kilogram. During the initial postoperative period, 11 per cent of the treated group and 58 per cent of the untreated group developed arrhythmias (either ventricular or supraventricular). Late arrhythmias occurred with equal frequency in both groups. Eight patients in each group developed ventricular irritability and were successfully treated with additional bretylium. Two patients could not be defibrillated postoperatively until bretylium was used. In a further study, 51 consecutive patients with acute myocardial infarction were treated, as well as eleven additional patients with refractory ventricular arrhythmias. Eight of these eleven patients had experienced one to five episodes of ventricular fibrillation. The patients were given 300 mg. of bretylium intramuscularly initially. Occasionally an additional 100 to 150 mg. of the drug was given intravenously. Doses were repeated every six hours for the first 48 hours with gradual dosage reduction over a four-day period. Supplemental doses of 100 mg. were given when needed. Of 37 patients admitted to the study with major ventricular arrhythmias, 6 (70 per cent) the arrhythmias were suppressed within four hours. Of the eight patients having recurrent episodes of ventricular fibrillation despite lidocaine infusion, fibrillation did not recur after bretylium therapy. Of 23 patients treated prophylactically, no significant arrhythmias occurred in 22. One patient died of ventricular fibrillation 5½ hours after the initial dose. These patients were kept supine and no significant hypotension was reported. Loose stools were frequent. Nausea and vomiting occurred with intravenous therapy and subsequently this route was used only for emergency situations. As bretylium's onset of action is slow and arrhythmias often resolve spontaneously in patients with acute myocardial infarction, more extensive studies are needed to confirm these optimistic findings. The claim that ventricular fibrillation may be reversed with intravenous bretylium is difficult to reconcile with the known delayed onset of action of the drug.

Other groups have been less enthusiastic although reporting successful experiences with bretylium. Ten patients with acute myocardial infarction were treated by Terry and associates,[7] all having ventricular arrhythmias resistant to conventional therapy. These patients were receiving digitalis and diuretics because of congestive heart failure. Five of the ten patients responded well to bretylium, 5 mg. per kilogram as a loading dose and 3 mg. per kilogram every 8 to 12 hours. We have used similar dosage schedules in 24 patients with acute myocardial infarctions. All had serious ventricular arrhythmias unresponsive to lidocaine and procainamide. None developed significant hypotension. Ten patients had no response, in six the results were equivocal, and 8 patients had complete control of the ventricular arrhythmias.

In a controlled study of alternate patients by Taylor and colleagues,[8] bretylium (300 mg.) was given every six hours to 63 men with acute myocardial infarction. The patients were allowed to use a bedside commode. Twenty-one developed significant hypotension requiring discontinuation of the drug. Two patients developed syncope when standing. In four patients, bretylium was discontinued because of vomiting. Thirty-eight patients received a full five-day course of medication and 38 patients were the control group. There were no significant differences in the incidence of ventricular tachycardia or ventricular fibrillation or in the mortality rates in the two groups. However, no treated patients

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Annotations

Treatment of familial hypercholesterolemia in children

Individuals with the heterozygous form of familial hypercholesterolemia (Type II hyperlipoproteinemia in the classification of Fredrickson and associates[1]) have greatly increased risk of death from ischemic heart disease[2] and often develop xanthomas and symptoms of coronary heart disease in early adult life. In the rarer homozygous form of the condition, xanthomas develop in early childhood and death from myocardial infarction is usual in childhood or adolescence. It has not yet been shown that lowering the serum cholesterol can delay the development of atherosclerosis in familial hypercholesterolemia. If, however, lowering the serum cholesterol has any effect, such treatment is likely to achieve the best results if started as early in life as possible, before atheromatous lesions have become too advanced.

We have used diet and clofibrate to treat 13 children with the heterozygous form of the disease. One child with the homozygous form has been treated for two years with diet, clofibrate, and cholestyramine.

Children with the heterozygous form

The nine girls and four boys (aged 2 to 15 years) were without symptoms and most had been referred for treatment because of family histories of coronary heart disease. None had xanthomas but one had corneal arcus. All had the biochemical features typical of familial hypercholesterolemia (increased beta-lipoprotein concentrations with increased serum cholesterol and normal serum triglyceride) and these abnormalities were also demonstrated in at least one parent.

*Table I. Heterozygous hypercholesterolemia. Effect of treatment**

Treatment	Patients			Dietary fat (Gm. per day) (mean and range)			Serum cholesterol	
	No. of children	Observations per child (8–? wk. apart) (mean and range)	Duration (mo.) (mean and range)	Ordinary fat	Flora margarine	Corn oil	Mg. per 100 ml. (mean and range)	Per cent reduction (mean and range)
Low-level corn-oil diet:	13							
Pretreatment		2	—	Ad lib.	0	0	370 (303–510)	—
Low-level corn oil		3 (3–8)	7 (3–22)	14 (7–22)	18 (8–44)	18 (8–36)	281† (192–355)	24 (9–46)
Comparison of low-level with high-level corn-oil diet:	7							
Pretreatment		2	—	Ad lib.	0	0	372 (303–434)	—
Low-level corn oil		3 (1–8)	8 (3–8)	18 (10–22)	33 (12–44)	11 (8–36)	296 (263–332)	21 (9–31)
High-level corn oil		4 (2–7)	3 (1–8)	18 (10–22)	33 (12–44)	57 (45–75)	308‡ (255–373)	18 (9–26)
Comparison of low-level corn-oil diet with the same diet plus clofibrate:	8							
Pretreatment		2	—	Ad lib.	0	0	381 (303–424)	—
Low-level corn oil		5 (3–8)	6 (3–8)	19 (10–22)	22 (12–44)	10 (8–18)	297 (263–332)	22 (9–31)
Low-level corn oil plus clofibrate		5 (4–6)	7 (4–8)	19 (10–32)	22 (12–44)	10 (8–18)	254§ (206–290)	33 (26–41)

*Reproduced with permission from Lancet Mar. 28, 1970.
†Significantly different from pretreatment ($p <$ .001).
‡Not significantly different from low-level diet.
§Significantly different from low-level diet ($p <$ 0.05).

developed supraventricular tachycardia while seven control patients did.

Optimal dose schedules for parenteral bretylium have not been determined and some of the clinical studies have been criticized as using inadequate amounts of the drug. Bacaner suggested initial doses of 5 to 10 mg. per kilogram intramuscularly with increments of 100 mg. hourly to a maximum of 2 Gm. He reports using up to 9 Gm. per day without major toxicity. Therapy should be continued at 5 mg. per kilogram every 4 to 6 hours. The dose should be less in patients with impaired renal function. Until blood levels have been correlated with clinical effects, no precise guidelines can be suggested. Oral bretylium has been reported effective in several isolated instances of recurrent ventricular tachycardia but further studies are needed. The drug should be used with caution in patients with valvular heart disease and congestive failure where sudden blood pressure fall or increase in pulmonary artery pressure may be dangerous. Because other antiarrhythmic agents may block the effect of bretylium, such agents should be discontinued when bretylium is started. The hypotensive properties of bretylium are minimized by keeping the patients supine; should hypotension occur, volume expansion and/or epinephrine, norepinephrine, or dopamine are effective. These agents should be instituted at low dose levels, as bretylium treated patients may be extremely sensitive to catecholamines.

Bretylium appears to be a promising antiarrhythmic agent lacking myocardial depressing effects. Although not always effective, it is of value in patients who despite routine therapy have recurrent ventricular fibrillation or life-threatening ventricular arrhythmias. It is our current opinion that lidocaine and procainamide are the first line of attack in treating these arrhythmias. Further investigation is needed specifically to determine optimal dosage schedules as well as to evaluate effects on patients with supraventricular tachycardia and conduction disturbances.

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unsaturated fatty acids because of the basic metabolic abnormality. Despite the lack of specific hypocholesterolemic effect of corn oil this and other oils rich in polyunsaturated fatty acids have an important role in dietary treatment, as they can be consumed without provoking the rise in serum cholesterol that would occur with the same amount of ordinary fat. Thus they can be used to improve the palatability of an otherwise low-fat diet, allowing food to be fried and baked and permitting the use of margarine these are important considerations in the acceptability of the diet. Their use also avoids the necessity for additional carbohydrate to maintain an adequate calorie intake. As shown in the figure and reported elsewhere low-fat diet with additional carbohydrate leads to an increase in serum triglyceride in children with familial hypercholesterolemia. If such an increase were maintained over long periods this might itself increase the risk of atherosclerosis.

Although clofibrate (chlorophenoxyisobutyrate) is used mainly in endogenous hypertriglyceridemia, it has been shown to reduce the serum cholesterol in familial hypercholesterolemia by about 10 per cent. Such reduction on its own is unlikely to be adequate treatment but in our study of children the addition of clofibrate to diet led to useful further reduction in serum cholesterol. Six children were given clofibrate (18 to 28 mg. per kilogram per day) when the "low-level corn-oil diet" was already established the serum cholesterol decreased further the mean reduction being 33 per cent on diet and clofibrate compared with 22 per cent on diet alone. Fredrickson and Levy[4] found that the combination of diet and cholestyramine is even more effective.

Child with the homozygous form

For the homozygous form of familial hypercholesterolemia no treatment has yet been found which will maintain cholesterol levels within or even near the normal range. Our patient first developed xanthomas at age 18 months, at which time her serum cholesterol was 1090 mg. per 100 ml. Both parents and her brother were shown to have the heterozygous form of familial hypercholesterolemia. Short-term trials of various forms of dietary and drug treatment were unsuccessful and the xanthomas increased in size and number. At the age of 9 years combined treatment with diet and drugs was started. The diet consisted of low intake of ordinary fat (9 Gm. per day) supplemented by a daily intake of 40 to 60 Gm. of oils and margarine rich in linoleic acid. the drugs given were clofibrate 500 mg. twice daily (40 mg. per kilogram per day) and cholestyramine 32 Gm. per day (in divided doses before meals). The serum cholesterol fell from 913 to a mean of 623 mg. per 100 ml. over a two-year period (32 per cent reduction). All her xanthomas decreased markedly in size and the smaller ones disappeared. Fecal fat excretion was normal despite the large dose of cholestyramine.

In our patient the skin lesions were distressing to both child and parents and for its cosmetic effects alone the results of treatment have been well worth while. We cannot say whether the development of arterial lesions has been influenced.

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A practical technique for superimposition of electrocardiograms on cineangiographic film*

With the development of precise cineangiographic technology it has become increasingly valuable to utilize this technique for physiologic studies of the intact heart as well as for definition of anatomic detail of structural intracardiac defects. The radiographic images are neither sufficiently precise nor exposed sufficiently frequently to permit use of cardiac chamber motion to indicate the onset, peak, or termination of events such as ventricular systole,

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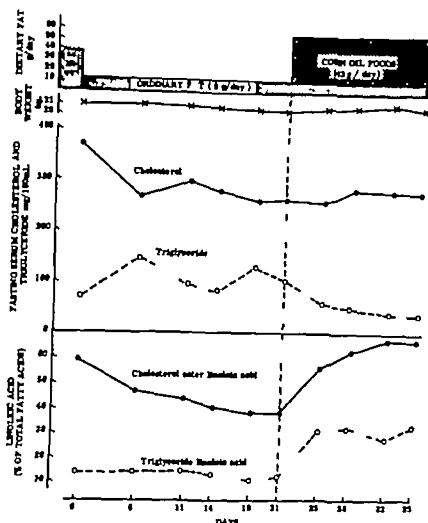


Fig *1* Effect on serum lipids of reduction in ordinary fat and subsequent addition of corn-oil foods in a girl aged 7 years with heterozygous hypercholesterolemia. During the period of low-fat diet the total calorie intake was kept constant with additional carbohydrate. (Reproduced with *permission from Lancet Mar 28, 1970.*)

They were treated with a diet low in ordinary fat (largely saturated) and supplemented with corn-oil foods, rich in polyunsaturated fatty acid (Table I) The *mean serum cholesterol was reduced from 370* to 281 mg per 100 ml (24 per cent reduction) The percentage reduction correlated negatively with the take of ordinary fat ($r = -0.66$, $p < 0.02$) but there was no correlation with the intake of corn-oil foods.

To demonstrate whether larger amounts of corn oil would have an effect on the serum cholesterol seven children were given a high-level corn-oil diet *In which 45 to 60 Gm of corn oil was added to* that already present in the low level diet this did not lower the serum cholesterol further

In one child treatment was started by reduction in ordinary fat without the addition of corn-oil foods (Fig 1) extra carbohydrate was given to maintain a constant calorie intake. On this diet the serum cholesterol fell from the pretreatment value of 372 to 268 mg per 100 ml *When corn-oil foods were* given instead of the extra carbohydrate the serum cholesterol rose slightly to 281 mg per 100 ml. The fasting serum *triglyceride concentration* rose during the period of high-carbohydrate, low fat feeding but decreased again after the introduction of *corn-oil* foods. The proportion of linoleic acid in the serum *cholesterol ester and triglyceride increased* during the corn-oil diet. The body weight remained constant (*within 1 Kg*) *throughout the periods of* dietary changes.

These results provide evidence that in patients with familial hypercholesterolemia the reduction in serum cholesterol on treatment with a diet in which much of the ordinary fat is replaced by corn oil is the result of the reduced intake of ordinary fat. *We found no specific hypocholesterolemic effect of* corn oil in our patients. Corn oil added to the diet *of healthy adults has been shown to lower the serum* cholesterol[3] but in the three adults with familial *hypercholesterolemia studied by Strisower and* associates[4] no significant change was found. One explanation for the difference in response may be related to the fatty acid composition of corn oil which contains appreciable amounts of saturated and monounsaturated as well as polyunsaturated fatty acids. In familial hypercholesterolemia the additional intake of saturated fatty acids from eating corn oil may nullify any specific hypocholesterolemic action *of the polyunsaturated fatty acids. Another* explanation may be that patients with familial *hypercholesterolemia are unresponsive to poly-*

the P waves, QRS complexes, and T waves, is readily discerned on the cine film. Fig. 2 is composite of three consecutive 35 mm. cine frames exposed t intervals of 16 7 msec. (60 frames per second) which display the motion of the radiopaque dot during portion of QRS complex. When viewed in motion, the resulting image of the electrocardiogram closely resembles that of a oscilloscope sweep without the image persistence of the usual oscilloscope display

This inexpensive and practical technique provides an excellent image of the electrocardiogram presented in real time superimposed on cineangiocardiographic film.

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"Pacemaker heart sound ' caused by diaphragmatic contractions

The pacemaker heart sound was first described by Nager and associates[1] in 1965 and may be represented as high-frequency generally high-intensity sound, occurring about 6 msec. after pacemaker artefact. Although initially it was believed to be of intracardiac origin, Harris[2] and others[3-5] have presented evidence favoring an extracardiac skeletal muscle site. The failure to record an intracardiac sound, an absence of an early rise in ventricular pressure coinciding with the outward movement in the apex cardiogram, the recording of similar sound by experimental pectoral and forearm muscle stimulation, nd the elimination of the sound by a neuromuscular blocking agent ll support this conclusion.

I tercostal muscle stimulation, due to spread of lectrical current from nearby pacing catheter has been implicated in the origin of the sound because actual t itchings of these muscles may occasionally be seen and recorded t the time of the extra so nd.[2,3,4] A pacer heart sound in the absence of overt contractions could result from contractions of only the internal intercostal or subcostal muscles. Kramer and associates, although indicating that intercostal muscle contraction may be involved, have show similar pacemaker sound to be present hen pectoral muscle contraction occurred in one patient, following current leak t the site of an indifferent lectrode. Visible muscle contractions were lso present and the high-intensity pacemaker sound was heard over the entire precordium.

Although it is know that the diaphragm may be stimulated during right ventricular pacing, all reports have been definite in pointing out that diaphragmatic timulation could not be the cause of the pacer heart sound. However we recently udied patient with prominent pacemaker heart sound hose characteristics f vor its origin in intermittent contractions of the left hemidiaphragm.

This patient, 77 year-old oman, as first seen in the emergency room of The University of Texas Medical School t San Antonio-Bexar Cou ty Teaching Hospital because of recent prolonged episode of dizziness associated with some dyspnea. Occasional dizzy spells and palpitations had also occurred during the previous 12 months

An electrocardiogram taken on admission showed complete sinoatrial block with junctional rhythm t the rate of 45 per minute nd nonspecific ST T wave abnormalities. Following insertion of temporary demand type pacing catheter through the left external jugular vein and pacing for six days, her symptoms improved significantly However repeated electrocardiograms, off pacing, failed to show any sinus node activity and her heart rate remained below 50 per minute. Because of her symptoms, electrocardiographic findings, and response to temporary pacing, permanent pervenous QRS inhibited demand bipolar pacemaker was inserted into the apex of the right ventricle. The temporary pacing catheter on standby function, was left in the outflow tract of the right ventricle to be removed in three to four days after table function of the permanent unit was assured.

Fluoroscopic observation revealed the permanent catheter tip to be in good wedged position, although somewhat inferiorly located over the diaphragmatic aspect of the right ventricle. The day after implantation rhythmic contractions of the left hemidiaphragm synchronous with the heart rhythm ere noticed, particularly prominent on expiration, and uscultation of the heart revealed loud, presystolic clicking sound heard all over both the anterior and posterior chest. No intercostal muscular contractions were observed, although these ere looked for in some detail. Posteroanterior and lateral chest films were obtained t review the pacemaker catheter position, and these disclosed that the permanent pacing catheter was located t the posterior inferior apical region of the right ventricle in close proximity to the left hemidiaphragm. The temporary catheter was located more anteriorly near the outflow tract of the right ventricle During fluoroscopy the left hemidiaphragm contracted constantly with the heart when pacing was carried out through the permanent catheter During deep

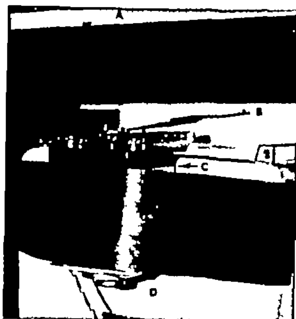


Fig. 1. View under cardiac catheterization table (*A*). The lucite stylus (*B*) and galvanometer (*C*) are mounted on the collimator (*D*).

Two general approaches have been used to provide precise knowledge of the time within a cardiac cycle at which individual cineangiographic frames were recorded. One approach superimposes either the image of an oscilloscope or a mechanical marker on the cine film; the other marks a physiologic recorder for each cine frame.

These approaches have been variably successful, but often involve expensive components and circuitry, loss of some cineangiographic information, or the necessity of correlating information recorded on two media. We have devised an inexpensive and easily applied technique by which the electrocardiographic signal can be directly superimposed on cineangiographic film.

An electrocardiographic cable was modified to conduct the signal in parallel to the physiologic recorder in use in the laboratory and to a standard Hewlett Packard Model 500 Electrocardiographic Recorder. The signal from the driver amplifier stage of the Model 500 is diverted through an extension cable to a separate Model 500 galvanometer. The Model 500 can be quickly converted simply by unplugging the extension cable and plugging in the original galvanometer. The standard stylus was removed and substituted by a radiolucent lucite rod 2 mm. in diameter and 10 cm. length. A 1 mm. diameter lead ball was glued to the distal end of the lucite rod. The galvanometer and its radiopaque tipped stylus was then placed under the surface of the x-ray table. The galvanometer is firmly mounted on the collimating cone of the x-ray tube. The opaque lead tip of the stylus extends into the primary x-ray beam emanating from the anode (Fig. 1). In this way the radiopaque image of the lead is superimposed as a small radiopaque shadow on the input and output phosphors

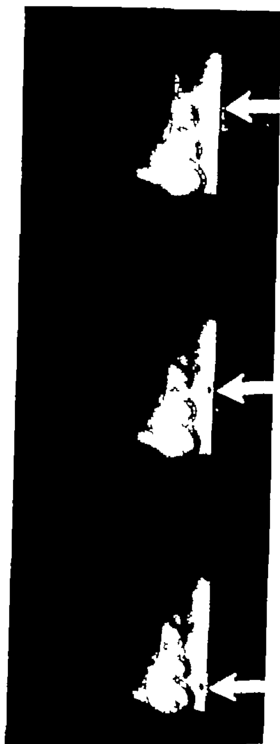


Fig. 2. Three consecutive cine frames. Each displays the cardiac silhouette. The radiopaque spot on the tip of an electrocardiographic stylus shifts position (arrows) from frame to frame as a QRS complex is inscribed.

of the image intensifier tube. The sensitivity and the position of the lead dot can be adjusted using the control panel of the Model 500 amplifier. The direct information of the electrocardiographic tracing is displayed as motion of the stylus and, therefore, as motion of the radiopaque dot. In this way the entire electrocardiographic complex, including

Hewlett Packard, Inc., Catalogue No. 626, $150.00.

Hemodynamic spectrum of left ventricular failure in experimental myocardial infarction

I recent decades many experimental models of coronary disease have been developed in an attempt to elucidate the pathophysiology of myocardial infarction. The aim has been to simulate the syndrome of left ventricular failure and/or shock as it occurs in man secondary to acute myocardial infarction. An experimental model identical to human coronary artery disease is still not reality; however progress has been made in many areas from study of nonatherosclerotic models of myocardial infarction.

Regional myocardial ischemia has been produced by obstruction of either one or several coronary branches. These studies have invariably been carried out in anesthetized animals. A characteristic hemodynamic picture has emerged. Typically there is marked decrease in cardiac output and arterial pressure, relatively minor elevation of left ventricular filling pressure, and no change in heart rate. Studies of diffuse myocardial ischemia using microemboli have yielded similar results and often have brought about state of shock.[1-9] However in these studies it has been recognized that the response to coronary ischemia may vary with the anesthetic agent used[9] furthermore, the pertinence of physiologic observations made on the circulation under anesthesia has been called into question.[10]

Recently in our laboratory method of occluding major coronary vessel in the awake animal has been developed and utilized for various pathophysiologic studies. [11] I contrast to anesthetized dogs, single vessel coronary occlusion in the awake animal is characterized by onset of sinus tachycardia, decrease in stroke volume, and marked elevation of left ventricular filling pressure. Aortic mean pressure usually remains stable or rises and cardiac output is well maintained. When failure is made more severe by partial constriction of second major coronary vessel, heart rate and left ventricular end-diastolic pressure increase further cardiac output decreases slightly but significantly but aortic mean pressure remains normal. Acute pulmonary edema may occur but not the shock syndrome.[16]

Thus the circulatory response t left ventricular failure resulting from coronary occlusion is different in the anesthetized and unanesthetized state. I the anesthetized animal adaptations to left ventricular failure result in low ventricular filling pressure, low cardiac output, and reduced aortic pressure. I the awake animal left ventricular failure is manifested by high ventricular filling pressure and maintenance of cardiac output and aortic pressure, which are normal or nearly so. The reason for this difference in circulatory response is not known t present. Anesthesia may influence autonomic reflexes and thereby result in tachycardia and altered arteriolar and venomotor tone. Anesthesia may also directly depress the myocardium, or may even have direct effects on the vasomotor center.

Recently it has been shown that high percentage of patients with myocardial infarction have hemodynamic evidence of left ventricular failure, in terms of elevated pulmonary arterial or left ventricular end-diastolic pressure, even in the absence of overt congestive failure, shock, or pulmonary edema.[17,18] These findings in patients are remarkably similar to those observed in the awake dog with myocardial infarction. Evidently in both human beings and in the experimental canine preparation circulatory adjustments following myocardial infarction often maintain aortic pressure and cardiac output even t the expense of increased cardiac work, ventricular dilatation, and presumably high levels of myocardial oxygen consumption. These results also suggest that the intact awake dog with coronary occlusion provides model more closely analogous to human myocardial infarction with mild t moderate left ventricular failure than has heretofore been available.

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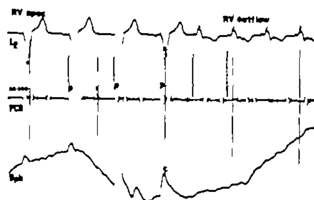


Fig. 1 Simultaneous recordings of the electrocardiogram (L_2) apical phonocardiogram (*PCG*) and diaphragmatic (*Dph*) contractions (*C*) When the permanent apical demand pacemaker is suppressed by turning on the temporary outflow tract unit, the pacemaker heart sound (*P*) and the diaphragmatic contractions are el minated

inspiration and descent of the diaphragm pacing continued however diaphragmatic contractions and the pacer heart sound d sappeared No diaphragmatic contraction or extra sounds were present when pacing wa performed with the temporary catheter

These findings are demon trated graphically n Fig 1 and illustrate how the production of the extra sound and diaphragmatic contraction are critically related to the site of right ventricular pacing With apical pacing through the permane t catheter the pacemaker heart sound occurs prior to the first heart sound and synchronously with the contraction of the left leaf of the diaphragm When the permanent pacing un t is overdriven by the external temporary unit, ventricular timulation orig nates from tl e right ventricular outflow tract (note difference in paced electrocardiogram) and no diaphragmatic contractions or pacemaker heart sound re apparent The diaphragmatic contractions produced a generalized sudden movement of the chest l ut no localized twitching of the chest wall could be seen at any time

A comb nation of phonocardiography and external chest wall timulation (CWS) was also used to characterize the pacemaker heart sou d CWS at 130 per inute s ppressed the ternal QRS inhibited demand pacemaker (85 per mi te) and the pacer sound which wa so readily apparent d ring internal paci g disappeared similarly the d phrag matic contractions were also suppressed

The pacemaker heart sound was more prominent than any we have ever heard before and it was audible n t only over all the chest, b t in the upper abdomen and even in the lumbar area. It was possible to hear and record this sound ynchronously with the pacer artefact, in areas in which no other heart sounds could be heard indicating ts great intensity and wide transmission.

In our patient, then no visible or recordable localized intercostal muscle contractions were oted however prominent left hemidiaphragmatic contractions occurred coincident with each pacer heart sound (Fig 1) X rays and fluoroscopy demonstrated that the permanent pacing catheter was away from the chest wall in close proximity to the diaphragm. When pacing was performed through a temporary catheter in the outflow tract (in fact, closer to the intercostal muscles) no extra sound or muscle contraction was present. With a deep inspiration and separation of the heart and the diaphragm, or using external chest wall stimulation, contractions of the diaphragm and the pacer sound were eliminated In addition the intensity of this sound is consistent with vibrations from a large muscle mass (the diaphragm) and is analogous to the increased intensity of the sound in the case of Kramer and colleagues, when a large pectoral muscle was stimulated Therefore we believe that this loud sound in our patient is secondary to diaphragmatic contraction.

This fact, along with previous studies, indicates that the pacemaker heart sound is not specific in its origin but may be initiated by electrical timulation of any skeletal muscle in proximity to a pacing unit.[3,4,5] In most patients with the extra sound only benign contractions of the intercostal muscles are present However pectoral muscle or diaphragmatic stimulation may occur and i this situation may indicate pacemaker malfunction malposition, or even myocardial perforation

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Letters to the Editor

Method for correction of the vectorcardiogram for body surface area

To the Editor:

It has been shown that the magnitude of the vectorcardiogram (VCG) depends upon body dimensions.[1-4] Our results showed that the X and Z dipole moments are proportional to the thoracic surface area, and that the vertical, Y component is proportional to thorax cross-sectional area. Thus

$$M_x = G_x kHPV_x \quad (1)$$

$$M_y = kAV_y \quad (2)$$

$$M_z = G_z kHPV_z \quad (3)$$

where V_x, V_y, and V_z are the measured voltages, k = thoracic conductivity, H = effective vertical height of thorax, P = periphery, and A = cross-sectional area of the thorax. G_x and G_z are factors used to correct for the attenuation of the resistance network.

In order to express Eq. 2 in the same form as Eqs. 1 and 3, we define the quantity T by

$$T = A/HP \quad (4)$$

Then Eq. 2 becomes

$$M_y = TkHPV_y \quad (5)$$

Our lead system[5] has potentiometers to adjust for body dimensions. Values of G_x and G_z are tabulated and are used to set the amplifier gains. These results have been exhaustively tested by artificial dipole experiments and by integration of potentials over the body surface.

It is suggested that other lead system voltages be multiplied by similar factors. This process should produce numerical values which convert voltage to dipole moment, and take body size into account. Then, for any lead system

$$M_x = K_x kHPV_x \quad (6)$$

$$M_y = K_y TkHPV_y \quad (7)$$

$$M_z = K_z kHPV_z \quad (8)$$

For a given lead system, the multiplying factors K_x, K_y, and K_z must be determined experimentally, e.g., by artificial dipole measurements.

I have found these K factors, for the Frank and McFee systems, from an experiment in which an artificial dipole was placed in an accurate plexiglas thorax model. Electrodes corresponding to these systems were placed on the model, and appropriate resistance networks were used. The dipole was set up in the X, Y, and Z directions, at 18 to 21 different locations. The X, Y, and Z ranges of dipole location were 12, 10, and 9.5 cm., respectively. The experimental value of dipole moment (current × pole separation) was 3.48 ma-cm. The model was filled with fluid having a resistivity of 500 ohm-cm. The dimensions of the model were HP = 3253 cm.², A = 600 cm.², T = 0.184. For the Frank system, the mean value of V_x for the dipole in the X direction, for all dipole locations, was 2.47 mv. Substituting in Eq. 6,

$$3.48 = \frac{K_x(3253)(2.47)}{500}$$

from which K_x = 0.22. Table I lists mean values of voltage for X, Y, and Z directions of the dipole, as well as the multiplying factors, for the Frank and McFee systems. These multiplying factors should be used in Eqs. 6 to 8.

To determine thoracic surface area, the periphery P is multiplied by the effective height, H. H = the vertical distance over which there is a variation in the electrocardiogram (ECG). It can be determined from bipolar voltage measurements between pairs of points and finding the levels at which the variation is very small. A good approximation is to use the distance between the top of the shoulders and the anterior superior iliac spine.

The periphery can be found from the routine chest measurement, or the periphery at three levels can be averaged. We approximate the thorax cross-section by an ellipse. The periphery and area of an ellipse are given by

$$P = 2\pi\sqrt{\frac{a^2 + b^2}{2}} \quad (9)$$

$$A = \pi ab \quad (10)$$

Where a = semi-major axis = half of left-right distance and b = semi-minor axis = half of anterior-posterior distance.

Once body dimensions have been measured, the amplifier gains may be set in proportion to the terms multiplying V_x, V_y, and V_z. The gain of the Y amplifier may be set to an arbitrary value, for example, 500. If A_x, A_y, and A_z are the gains of the X, Y, and Z amplifiers, then the gains are set such that

$$\frac{A_x}{A_y} = \frac{K_x}{K_y T} \quad (11)$$

$$\frac{A_z}{A_y} = \frac{K_z}{K_y T} \quad (12)$$

The output voltages will then be directly proportional to dipole moment.

A value of k = 1/500 ohm⁻¹-cm.⁻¹ can be assumed but if k can be measured, this value should be used instead. I still leave the results in terms of k because I am not convinced that present methods of measur-

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Emergency management of failing pacemakers

To the Editor:

In the interest of patient care and safety we would like to offer the following critical commentary on the article, "Emergency management of pacemaker failure by means of radio frequency energy" by Riccardo Benvenuto and Peter Mayer (AM. HEART J. 81:738, 1971).

This presentation, in most general terms, implies that the Medtronic external rate control, Model No. 5855, can be used to increase the output of standard pacemakers with depleted batteries. It later states that the authors usually use pulse generators of different types produced by the Medtronic Company, the type most frequently used being the so-called demand, or ventricular inhibited, pacemaker. It even suggests, without clearly defining the limits of suitability or utility that this safety measure may be made available to patients and their families for emergency use in case of sudden pacemaker failure outside the hospital. Late in the article the authors give the only clear hint that this may have limited applicability by suggesting the possibility of using the external rate control to augment failing pacemakers of different manufacturers than Medtronic.

In fact, the measure proposed was clinically applied to only six pacemakers, model number unspecified, but probably the Medtronic No. 5841. This particular pacemaker was specifically designed to be responsive to overdrive by the No. 5855 rate control as a method to override arrhythmias or as a test of ability to pace in a patient normally in sinus rhythm with R wave inhibition of output. It was discontinued from production by Medtronic Inc. in May 1970, the month this article was submitted for publication. The effect described by the authors will work only in some failure modes of the pacemaker model No. 5841, specifically if the defect is the failure of one or two battery cells or their equivalent. In this event, the residual energy to the oscillator or the output transistor becomes, by design, insufficient to drive the output switch, the output drops to zero or near zero, and the patient is protected against development of a runaway rate (an increase in timing circuit rate produced by a drop in battery voltage).

Application of the Medtronic control, model No. 5855, in this event, provides enough energy to the output transistor to trip the oscillator to drive the output switch, releasing the adequate residual energy in the surviving cells to pace at the controlled rate of the overdrive. If the battery failure is in the open circuit configuration, this effect will not occur.

There is a theoretic possibility that when applied where failure is due to a high threshold rather than to battery depletion, the control No. 5855 may effect further loss of pacing. We have not tested this clinically. However in preliminary bench tests of used but nonfailing pacemaker model No. 5841 pacing into a 500 ohm load, overdrive to 100 beats per minute resulted in a small drop in the oscilloscopically measured pulse amplitude in the first 0.5 msec., a shortening of pulse duration (from 1.8 to 1.5 msec.) and a drop of 20 per cent in total energy output per pulse.

The Medtronic models No. 5870 or 5870C and a few of the other early asynchronous pacemakers also respond with a rate increase to overdrive by the No. 5855 control. They do not, however have the circuit features that permit output augmentation by the overdrive. The new Medtronic asynchronous models No. 5861 and 5862C pacemakers do not respond at all to the No. 5855 control.

Of crucial importance in the Medtronic "demand" or ventricular inhibited" pacemaker is the fact that the No. 5842, which replaced the No. 5841 in May 1970, and the Nos. 5942 and 5943 introduced in 1971 interpret the output of the rate control No. 5855 as an R wave equivalent. If properly stimulated with an overdriving rate they will TURN OFF completely! If a potential for asystole exist this may precipitate an Adams-Stokes event. As regards other manufacturers we have used the Medtronic control No. 5855 as an alternate to the General Electric radiofrequency control to overdrive current models of General Electric R wave suppression demand pacemakers. This company advises that all their present radiofrequency responsive model will follow the Medtronic No. 5855 control but cautions that their circuits do not allow for any enhancement effect. In fact, all General Electric pacemakers respond to overdrive rate increases by a small drop in output, presently about 15 per cent from 70 to 130 beats per minute in the demand units. Information on this output drop with rate increase has been available for several years.

In tests of pacemaker function that we have been conducting for five years, we have found the Medtronic control No. 5855 more effective than the No. 5800 in transcutaneous stimulation of triggered pulse generators. Using these techniques, we have simulated R wave suppression and "turned off" the Medtronic pacemaker No. 5842, the Cordis Company Ventricor II and Stanicor the American Optical Company Cardiocare, and have disturbed the function of the new American Optical Company AV sequential pacemaker. The Medtronic No. 5855 control may inhibit the Medtronic pacemakers Nos. 5842, 5942, and 5943 whereas the control No. 5800 may not. In the Cordis Atricor (atrial synchronous) or Ectocor (ventricular synchronous) pacemakers, the output of the Medtronic rate controls No. 5800 or 5855 will be recognized by the pulse generators as an atrial or ventricular voltage respectively and they will respond to overdrive with a rate acceleration. With battery failure they cease to respond to this type of stimulation (a useful test of failure). The Biotronik pacemakers are similar to the Cordis. Fixed-rate pacemakers, unless designed to be responsive to a rate control unit, are not affected by either the Medtronic model No. 5800 or 5855 and, in any event do not exhibit augmentation.

In view of these data, it becomes obvious that the authors clinical advice on the basis of limited study may well result in dangerous usages by persons not in a position to judge critically for themselves. Overdriving and triggering, done under oscilloscopic or electrocardiographic (ECG) monitoring, has an extremely useful role in the knowledgeable function

Table I

Dipole direction	Frank		McFee	
	mr	m.f	mr	m.f
X	2 47	0 22	2 99	0 18
Y	41	1 20	2 95	1 00
Z	2 32	0 23	3 13	0 17

g average thorax conductivity are valid McFee and Rush consider that errors may arise because of the low-resistance muscular surface layer In our measurements of conductivity we found little change during respiration whereas the VCG itself showed significant respiratory effects.

These corrections do not increase the basic accuracy of a lead system which up to a point is a function of the number of electrodes used In addition values were determined from a thorax model of only one size and shape They do, however provide scaling factors which result in values closer to true dipole moment and which compensate for large variations in body size

In the artificial dipole experiment referred to above the ranges of values of the intrinsic component e g I for an X dipole were much greater in the Frank and McFee system than in our own lead system Also the ranges of the error components (e.g I and I for an X dipole) were also larger These errors were function of the dipole location and had both positive and negative values.

The multiplying factors listed in the table are tentative only For determination of more accurate values, experiments should be carried out on several different thorax models, and in vivo comparisons should be made between a given lead system and a highly accurate system.

Thoracic potential studies have shown that the distribution is very complex during portion of the QRS complex with two or more maxima or minima of potential occurring simultaneously It is difficult to see how a lead system with small number of electrodes can adequately sample and average this potential field to produce valid resultant vectors.

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An aid to left heart catheterization

To the Editor

From time to time we all occasionally come across helpful clues or innovations which are of considerable benefit to us in the practice of laboratory cardiology In December 1968 after we had been attempting for some time to maneuver a Judkins pigtail" ventriculography catheter into the left ventricular chamber (via right femoral percutaneous approach) the patient became quite interested in what we were doing and asked if he could observe the procedure. Our TV monitor is mounted directly behind and above the head of our catheterization table and within ten seconds following the patient voluntary hyperextension of his neck (without any lateral flexion or rotation) we successfully negotiated the aortic valve. Since that time, in over 250 left heart catheterizations, we have never been unable to catheterize the left ventricular chamber This includes patients who have been studied via retrograde catheterization of the right brachial artery and also applies to other types of catheters such as the NIH the Lehman ventriculography and the Sones. The experience also includes 13 patients with valvular aortic stenosis.

As implied above, the most dramatic application of this technique of having the patient hyperextend his neck has been with the use of the pigtail type of ventriculography catheter introduced via the femoral artery by means of the Seldinger technique. The mechanism by which this maneuver works is unclear to me although it would seem reasonable to presume that it permits some straightening of the ascending aorta allowing the catheter a slightly different direction of entry into the left ventricular cavity In summary I feel that this method offers a simple safe, and consistently effective maneuver for catheterization of the left ventricular chamber

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Book reviews

ISCHEMIC HEART DISEASE, Boerhaave Series. Edited by J. H. DeHaan, M.D., H. C. Hemker, M.D., and H. A. Snellen, M.D. Baltimore, 1970, The Williams & Wilkins Company. 439 pp. Price $23.75.

This book records the proceedings of the Boerhaave Courses on ischemic heart disease held in Leiden, The Netherlands. The participants are numerous and of international reputation. Problems relating to myocardial ischemia are covered rather extensively in chapters devoted to pathogenesis, epidemiology, diagnostic methods, physical activity, prevention, and treatment. There is little, if anything, new in this publication although the book does gather valuable information on this important disease. The volume is well organized and reveals many of the unanswered problems related to ischemic heart disease. On initial evaluation the reader is impressed with the lack of reliable objective data concerning these important problems. Although much of its material is highly opinionated, this remains a valuable book on an extremely important subject.

ISCHEMIC FORMS OF VENOUS THROMBOSIS, Phlegmasia Cerulea Dolens Venous Gangrene. By Henry Haimovici, M.D. Springfield, Ill., 1971, Charles C Thomas, Publisher. 230 pp. Price $23.00.

In this small volume Haimovici has gathered aspects of the important problems of ischemia of the limbs in association with venous thrombosis. Physicians too often fail to realize the role of arterial vasoconstriction in association with diseases of the veins such as venous thrombosis. The ischemia can be intense enough to produce gangrene even though the lesion is primarily venous; Haimovici has clearly emphasized this problem in his book. The monograph consists of 11 chapters comprising definition of terms, history, etiology, clinical manifestations, pulmonary embolism, pathophysiology, diagnosis, prognosis, and treatment. This book summarizes the point of view of an experienced vascular surgeon but it should interest nonsurgeons as well.

POLARCARDIOGRAPHY. By Gordon E. Dower, M.B., B.S., F.A.C.C. Springfield, Ill., 1971, Charles C Thomas, Publisher. 314 pp. Price $31.50.

Dr. Dower has emphasized polarcardiography for a number of years in his research in electrocardiography. This monograph brings together not only his own ideas and contributions but the theory and problems related to this aspect of electrocardiography. The volume includes chapters devoted to the heart vector and its coordinates, the variations of polarcardiography in the normal subject, its variations with diseases of the heart, recorders and instrumentation, and analysis of data. An appendix of tables of p percentiles and conversion of latitudes and longitudes to angles between two vectors are included.

This book is well written and presents clearly and accurately the concepts of polarcardiography. However, the application of polarcardiography to clinical medicine is yet to be established. Unless the method is appreciably easier and more practical than electrocardiography and will repeatedly detect lesions of the heart that electrocardiography can not detect, the clinician will not accept this procedure in his practice. Electrocardiography as conventionally employed today is extremely practical and helpful. The major difficulties or inaccuracies in electrocardiography reside in the poor fidelity of the direct writers and in errors of interpretation. An example of the latter may be seen in Fig. 9.1A on p. 84. A V lead is shown to be compatible with lateral wall infarction but Lead I and V are not. This reviewer has seen V lead with this configuration in which the heart did not reveal a lateral wall lesion at autopsy. Furthermore, the patterns of the electrocardiograms in Figs. 9.1A and 1B are significantly different. This example illustrates how the interpretations of the ECG can vary widely among those who view them. This is nevertheless a good book and Dr. Dower has done an extremely fine job. He is obviously an expert on polarcardiography. The reader must remember, however, that this concept is still in the research stage. Its application to clinical practice is far from being established. Much more evidence of its usefulness in experimental laboratory and clinical cardiology needs to be gathered.

CORONARY HEART DISEASE. Edited by Henry I. Russek, M.D., and Burton L. Zohman, M.D. Philadelphia, 1971, J. B. Lippincott Company. 502 pp. Price $20.00.

This monograph is a collection of papers presented at meetings held in New York City on Dec. 13 to 15, 1968, under the auspices of the American College of Cardiology and St. Barnabas Hospital. The papers vary in length and unfortunately in quality. Nevertheless, the book contains a wealth of useful and important information and Drs. Russek and Zohman have rendered an excellent service to cardiology first by organizing the meeting and then by producing this volume. The editors' own papers on the natural history of coronary atherosclerosis contain much important data. Their contribution illustrates how variable the life expectancy of patients is in different medical centers and how difficult it is to know the precise survival rate for patients with angina pectoris and myocardial infarction. Unfortunately, the history of coronary artery disease as outlined by George Griffith is inaccurate in many

testing of demand and synchronous pacemakers. The ability to suppress output (presently unique to an R wave inhibited instrument) is also of value when the patient is pacing in the fixed rate mode and it becomes important to examine the underlying rhythm or character of the ECG. But augmentation of energy output in pacemaker failure by overdrive with a Medtronic No. 5855 control is limited to a selected type of failure mode in the now discontinued Medtronic model No. 5841 pacemaker.

Finally, the authors' alarmed statements in regard to emergency pulse generator replacement in case of battery failure are out of date and out of place. Considered opinion has long held that (1) a pacemaker patient appropriately and carefully followed should always have an elective procedure without crisis and only very rarely requires emergency management for battery depletion pacing failure[8] (2) that rapidly applied, relatively safe temporary transvenous bipolar pacing long ago replaced emergency surgical exteriorization of the pulse generator[10, 11] and (3) that competitive pacing need not occur in an appropriately implemented situation and, in any event, is not normally a significantly dangerous occurrence.

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Reply

To the Editor:

We are pleased that the authors of the preceding letter recognize the limitations of the radiofrequency effect discussed by us. These limitations are clearly indicated in our article.

The extensive material the authors quote in their letter is self-explanatory. Two points, however, require comment. First, one wonders why with five years' experience Dr. Escher and her associates did not describe the augmentation effect previously. Second, the statement that "overdriving and triggering done under oscilloscopic or electrocardiographic monitoring has an extremely useful role in the knowledgeable function testing of demand and synchronous pacemakers" is the exact error our article warns against. In testing the function of an inhibited pacemaker, the augmentation of energy which may be produced by use of the rate control unit may indicate that a failing pacemaker is still functioning when indeed the batteries are dangerously depleted.

We recognize the authors' personal interest in procedures which will make emergency replacement of pacemakers unnecessary, but, as a practical fact, this situation still occurs rather frequently. The series reported by the authors themselves at the meeting of the American College of Cardiology this year indicated a 7 per cent error in accurately predicting pacemaker failure prior to replacement. In a total of 100 cases this represents 7 patients requiring our radiofrequency external stimulation if an emergency procedure is to be avoided. It is exactly to safeguard these patients that our efforts are directed.

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Book reviews

Ischemic Heart Disease, Boerhaave Series. Edited by J. H. DeHaas, M.D., H. C. Hemker, M.D., and H. A. Snellen, M.D., Baltimore, 1970, The Williams & Wilkins Company. 439 pp. Price $23.75.

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respects, not only typographically (e.g. spelling of George E. Fahr's name, I. I. Grant for 1951 should be R. I. Grant, etc.) but it is especially inaccurate in the history of vectorcardiography, electrocardiography, pathology, and vasodilators. *It is at any rate hazardous* to attempt to fi t the hi tory of any aspect of medicine since the history of *medicine is replete with error and historians* differ substantially in their interpretations of event and contributions too often what *is accepted a a fact today* becomes an error tomorrow. In spite of this this i a very useful book that contains important pragmatic information and advice for the practicing physician.

MY LIFE AND MEDICINE. An Autobiographical Memoir. By Paul Dudley White. Boston. 1971. Gambit Incorporated. 269 pp. Price $6.95.

Paul White, the grand cardiologist, has written a warmly human book. A he narrates some of the experiences in hi exciting life that impressed him most, the reader is enabled to see the influences that shaped Paul White's career as doctor and cardiologist. Many of his boyhood experiences will strike a familiar chord in his readers. Paul's father, *hardworking and dedicated, set an example* that the doctor wa to follow all his life. Dr. White seem much more impressed by the *important patients* he has treated in the course of his career than by his own efforts; conversely, this reviewer was most affected by the doctor's great humanity as manifested in his desire to help young physicians and all those who came to him for assistance. Of course hi interest i international medicine a well as his prominent patients eventually brought him worldwide recognition in the field of cardiology. This interesting volume is heartily recommended to students, house officers, and all doctors, who will find it a fine addition to their library. Mrs. White and all of Paul friend and close associates must be particularly pleased with his autobiography; this reviewer certainly was.

Books received

CARDIOVASCULAR CLINICS, Vol. No. 3. International Cardiology. Edited by Albert N. Brest and Paul Dudley White. Philadelphia. 1971. F. A. Davis Company. 301 pages. Price $10.00.

HYPERTENSION, Vol. XIX. Salt, Hormones and Hypertension. Proceedings of the Council for High Blood Pressure Research, Cleveland, October 16 and 17, 1970. Edited by Patrick J. Mulrow. New York. 1971. American Heart Association. 191 pages. Price $5.00.

ELECTRICAL STIMULATION OF THE HEART IN THE STUDY AND TREATMENT OF TACHYCARDIAS. By H. J. J. Wellens. Baltimore. 1971. University Park Press, 142 pages. Price $10.00.

PORTRAIT OF APHASIA. By David Knox. Detroit, 1971. Wayne State University Press, 120 pages. Price $5.95.

PRINCIPLES OF DRUG ACTION—*The Basis of Pharmacology*. By Avram Goldstein, Lewis Aronow and Sumner M. Kalman. New York, 1968. Harper & Row. 884 pages. Price $18.50.

SELECTIVE BRONCHIAL AND INTERCOSTAL ARTERIOGRAPHY. *By A. S. J. Botenga. Baltimore. 1970.* The Williams & Wilkins Company. 187 pages. Price $32.50.

TEXTBOOK OF MEDICINE, Ed. 13. Edited by Paul B. Beeson and Walsh McDermott. Philadelphia. 1971. W. B. *Saunders Company*. 1923 pages.

Announcements

Heart Sounds and Murmurs

The Graduate School of Biomedical Sciences of the University of Texas will present an internal review *program entitled* "Heart Sound and Murmurs" to be delivered on December 7 through December 9, 1971, in Houston, Texas. The guest lecturer will be W. Proctor Harvey, M.D., Professor of Medicine and Director of the Division of Cardiology, Georgetown University Hospital, Washington, D. C. *Dr. Harvey* is also past president of the American Heart Association.

For further information write to: Office of the Dean, *The University of Texas Graduate School of* Biomedical Sciences at Houston, Division of Continuing Education, P. O. Box 20367, Houston, Texas 77025.

Ninth Annual Cardiology Seminar

A seminar on selected topics i cardiology will be held in Acapulco, Mexico, on December 2 through December 5, 1971, at the Princess Hotel. Sponsored by the Rogers Heart Foundation, the seminar will be under the direction of Henry J. L. Marriott.

For further information, write to: The Rogers Heart Foundation, St. Anthony Hospital, St. Petersburg, Fla.

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Acknowledgment to reviewers

The Editors wish to express their thanks and appreciation to the following who have aided in the review of manuscripts during the past year

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Editorial

Environmental temperature and the incidence of myocardial infarction

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It has been indicated that the number of patients with myocardial infarction (MI) admitted to the hospital and the death rate from MI vary from one season to another. In the cold and temperate zones the number of patients with MI is particularly high during the winter months.[1-3] On the other hand, in the warm zones more patients are admitted to hospitals with infarctions during the hot summer months than during the cooler winter months.[4] In most studies the incidence of MI has been compared with the mean monthly temperature, as the mean temperature of one month may vary greatly in certain areas. The variations which may occur in the mean temperatures of individual days within one month are still greater. An acute change in environmental temperature may apparently provoke a heart attack in both warm[4] and cold climates and thus a clearer picture might be obtained of the incidence of MI if it were correlated with the environmental temperature prevailing at the time of the attack. On this basis, the effect of mean daily temperatures on the number of subjects admitted for MI was studied by Sotaniemi, Vuopala, Huhti and Takkunen of the University of Oulu, Finland.

The investigations were carried out in a subarctic area where the mean annual temperature during the last fifty years has been about +2° C. The hospital admissions for MI were investigated over a period of four years (1965 to 1968). The days were divided into seven groups according to the mean daily temperature. The number of patients with MI admitted to the hospital each day was ascertained and they were divided into the groups mentioned. The death rate in each group during the hospital stay was calculated.

The number of admitted patients with infarction was lowest on days with mean temperatures near the mean annual temperature. On days either colder or warmer than this, more patients were admitted to the hospital. Within a limited area people seem to be adapted to environmental temperatures closely resembling the mean annual temperature, and our results indicate that deviations from the mean temperature toward either colder or warmer conditions increase the number of hospital admissions for MI and apparently also the incidence of its occurrence. Our findings agree with the results which show that in the cold and temperate zones a fall of temperature and in the warm zones a rise of temperature brings about an increase in the incidence of MI. Differences in national habits and customs may be the reason why it has not been possible to indicate the above mentioned correlation in all studies. It is also possible that the mean monthly temperature and its variations are too rough a unit to express changes in the

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incidence of an acute illness When the patient material we investigated was divided into only two groups according to the mean temperature of the month during which the illness occurred (either below or above 0° C) no difference could be shown in the admission rate between these two groups

It has not been explained so far what causes the rise in the incidence of MI when the temperature deviates up or down from the ideal Anderson and Le Riche[2] thought it probable that the frequency of respiratory infections which increases as the weather becomes colder would indirectly increase the incidence of myocardial infarction also But it is difficult to relate respiratory infections with the fact that the infarction rate also increases when the environmental temperature rises and also in warm areas.[4] If respiratory infections did contribute to the increase in the frequency of MI it would be expected that the death rate would be higher among those patients who became ill on cold days than among those whose attack occurred on a warm day No clear difference of this type was noted in our work which in a way seems to suggest that the change of temperature would affect the heart more directly Our own study as well as Rose's[3] data suggest that the change of temperature affects the heart and the frequency of MI directly The matter could be further elucidated by investigating the occurrence of respiratory infections in patients with MI who died during different seasons and on whom autopsies were performed This kind of investigation has probably not yet been done The protein bound iodine[9] and serum lipids[10] of the plasma also vary according to the seasons, at least in areas where the alternation of seasons is clear These variations together with the changes which take place in people's eating habits clothing and spare time activities during the different seasons may also contribute to the changes in the incidence of MI

It can be asked whether our results as such have any significance for the practical treatment of patients During the last few years improved communications have made flights to the so-called sun beaches popular particularly in Scandinavia This means that within 8 to 12 hours one can fly from the $-30°$ C. of the North to a temperature of $+20$ to $+30°$ C in which case the change in environmental temperature may be 40 to 60° C Such a change of environment for even a short period can be considered extremely hazardous for elderly people The same question has been dealt with by Burch and Ansari[11] in their article On prescribing the climate.

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Observations on the mechanism of one type of so-called supernormal A V conduction

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Supernormal atrioventricular (A V) conduction is the term applied to the phenomenon in which conduction of impulses is better than expected. This phenomenon generally occurs during depressed states of A V conduction and the term applies not to conduction which is faster than normal but rather to conduction which is less abnormal or totally unexpected.[1] In this regard it is well recognized that supernormal A V conduction is an inappropriate term. Many clinical reports have appeared in which supernormal A V conduction has been postulated.[2-10] In 1924 Lewis and Master[1] reported a case of complete heart block in which atrial impulses which followed the QRS complex by less than 0 425 sec. or by more than 0 908 sec. failed to propagate to the ventricles while those atrial impulses occurring between these periods generally were conducted to the ventricles. Conduction within this limited period of the cardiac cycle was attributed to supernormal A V conduction. The prevailing view has been that supernormal conduction occurs within a limited period of the cardiac cycle and is a fundamental property of A V conduction. However Pick and associates[1] have emphasized the role which antegrade and retrograde concealed conduction and unidirectional block play in the fundamental mechanisms explaining supernormal A V conduction. Likewise, Moe and associates[3] have suggested alternative mechanisms to explain most of the clinical reports of this phenomenon. During the course of premature atrial stimulation studies in our laboratory we have observed 11 cases which would be classified as supernormal A V conduction. In all 11 cases a "gap in A V conduction" was noted.[11] Premature atrial impulses occurring late in the cardiac cycle (i.e., long R P intervals) were conducted to the ventricles. At shorter R P intervals, A V conduction failed. When the R P interval was decreased further A V conduction resumed. It is the purpose of this report to provide evidence showing that these 11 cases of so-called supernormal A V conduc

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tion can be explained by the normal conduction characteristics of the A V nodal and His-Purkinje systems.

Methods

Right heart catheterization was performed in the postabsorptive nonsedated state. All patients were advised of the nature of the studies and a signed consent was obtained. All subjects had normal sinus rhythm at the time of study and were not taking any cardiac drugs. With the use of local anesthesia a tripolar electrode catheter was percutaneously introduced into the right femoral vein and fluoroscopically positioned in the region of the tricuspid valve. This catheter was used to record electrical activity of the bundle of His as previously described.[12] Similarly, a bipolar electrode catheter was introduced into an antecubital vein and fluoroscopically positioned against the lateral wall of the right atrium near its junction with the superior vena cava. The bipolar catheter was used to prematurely stimulate the right atrium at varying intervals synchronized off the preceding R wave.[13,14] Atrial stimulation was accomplished using a battery powered pacemaker which delivered impulses of 2 msec duration at approximately 1 to 2 × threshold. The interval from the onset of the atrial electrogram (*A*) or the stimulus artifact (*S*) when the atrium was prematurely stimulated to the His (*H*) deflection (i.e., the A H or S-H intervals) was taken as a measure of A V nodal conduction. The interval from the *H* deflection to the onset of ventricular depolarization (H V interval) was taken as a measure of His Purkinje conduction time. During premature atrial stimulation the interval between the onset of the sinus QRS complex and the premature stimulus is expressed as the R P interval. All records were taken on a multichannel oscilloscopic photographic recorder at paper speeds of 100 to 200 mm. per second. Attention was given to the proper grounding of all equipment.

Results

The phenomenon to be described in this report was observed in 11 of 70 subjects in whom premature atrial stimulation studies ... performed. The mechanism was the same in all 11 cases. Five of the 11 subjects had no evidence of heart disease. Four subjects had left bundle branch block (LBBB) and one patient with a normal QRS complex had arteriosclerotic heart disease with angina pectoris. All subjects had normal P R intervals (<0.20 sec.). Two illustrative examples are presented.

Fig. 1 is a recording from a 26-year-old normal male subject. Panels *A* to *D* demonstrate the results of premature atrial stimulation at progressively shorter R P intervals. In each panel the R R cycle lengths preceding the premature atrial depolarization are approximately the same (950 to 960 msec.). At a long R P coupling interval (Panel *A*) the premature atrial beat results in normal ventricular depolarization and is conducted to the ventricles with a slightly prolonged A V nodal conduction time (A H 130 msec.). At a shorter R P coupling interval, as shown in Panel *B*, the premature atrial beat fails to elicit a ventricular response. The premature atrial beat traverses the A V node with a slightly greater delay (A H 140 msec.), depolarizes the bundle of His, and conduction fails within the His-Purkinje system. When the R P interval was shortened further (Panel *C*) A V conduction resumes. The premature atrial beat encounters further A V nodal delay (A H 240 msec.) and arrives within the His-Purkinje system at a time when this system is less refractory. The QRS complex is slightly aberrant and the H V interval is prolonged to 60 msec. As shown in Panel *D*, A V conduction again fails when at a shorter R P interval the premature atrial beat encounters the effective refractory period of the A V node and is blocked proximal to the bundle of His.

Figs. 2 and 3 represent a continuous sequence of tracings and illustrate another example of so-called supernormal A V conduction recorded from a 67 year-old male patient with LBBB. The mechanism for failure of A V conduction followed by resumption of A V conduction is the same as in Fig. 1. Panel *A* depicts two sinus beats in which the *A H* and *H V* intervals measure 95 and 55 msec., respectively. As the coupling interval is shortened (Panels *B* and *C*) A V nodal conduction time increases (A H 155 msec.) and a ventricular response occurs. Panels *D* and ... demon



Fig. 1 So-called supernormal A-V conduction occurring in 26-year-old male subject. Each panel shows electrocardiographic Leads I and II. *HBE* refers to the His bundle electrogram tracing. *A* is the atrial electrogram, *H* the His deflection, and *V* the ventricular electrogram. *R-P* (380 to 190) refers to the coupling interval of the premature atrial beat and *R-R* (955 to 960) refers to the preceding cycle length. *S* denotes the stimulus artifact delivered to the right atrium.

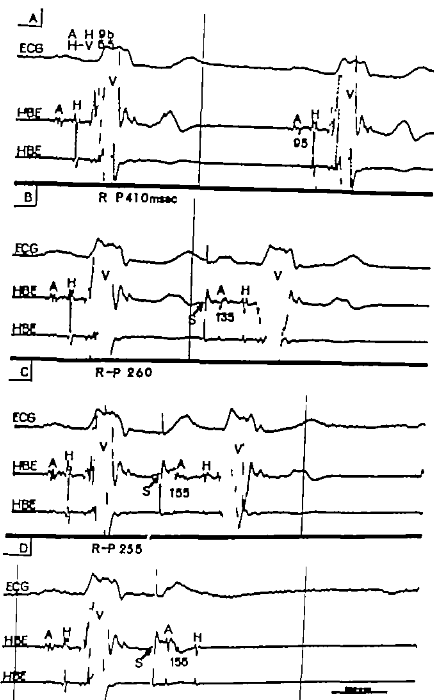


Fig 2 Abbreviations are the same as in Fig 1 *ECG* is electrocardiographic Lead II As in F g 1 the sinus cycle lengths preceding the premature trial beat were the same for this figure and Fig 3

strate that at R P coupling intervals between 255 and 215 msec. A V conduction fails distal to the bundle of His. As the R P coupling interval is shortened further (Panels *F* to *H*) A V nodal conduction time progressively increases (310 to 490 msec) and A V conduction resumes When the R P coupling was shortened further than that shown in Panel *H* of Fig 3 the atrium was refractory and A V conduction again failed

The zone of so-called supernormal A V conduction ranged between 30 and 80 msec. and was limited by the effective re fractory period of either the A V node (Panel *D* of Fig 1) or the atrium

Discussion

The transmission of impulses from the atria to the ventricles involves conduction along several specialized fiber types which include the A V node the bundle of His the right and left bundle branches and the Purkinje network. The effe ive re

fractory period of each of these structures is different.[13] Thus failure of impulse transmission will occur for the most part in that portion of the system which has the longest effective refractory period. Previous studies in man have demonstrated that atrial impulses may be delayed or blocked proximal or distal to the bundle of His.[14] When atrial impulses occurring at relatively long R P intervals are blocked proximal to the bundle of His (within the A V node) it follows that the more premature impulses (shorter R P interval) will likewise be blocked proximal to the bundle of His. Under these circumstances the effective refractory period of the A V node is longer than the effective refractory period of the His-Purkinje system. However as in our 11 cases, when less premature atrial impulses are initially blocked distal to the bundle of His, the effective refractory period of the His-Purkinje system is longer than that of the A V node If A V nodal conduction time can be sufficiently prolonged so as to allow the His-Purkinje system to become more completely repolarized then the heretofore blocked impulses can be conducted to the ventricles. Such a condition was attained when the atrium was more prematurely stimulated At shorter R P intervals the premature atrial beats entered the A V node during its relative refractory period A V nodal conduction time was prolonged (increase in A-H interval) and a ventricular response occurred because excitability of the His-Purkinje system had recovered When the atrial impulse arrives in the His-Purkinje system during the latter's relative refractory period the ventricular response may reflect aberrant intraventricular conduction Not all patients who demonstrate block in the His-Purkinje system at a given R P interval will resume A V conduction at shorter R P intervals. Resumption of A V conduction at shorter R P intervals will not occur if A V nodal conduction delay is not of sufficient magnitude so as to prevent the atrial impulse from arriving within the His-Purkinje system during the latter's effective refractory period Also, resumption of A V conduction will not occur at shorter R P intervals if the effective refractory period of either the A V node or atrium is reached before

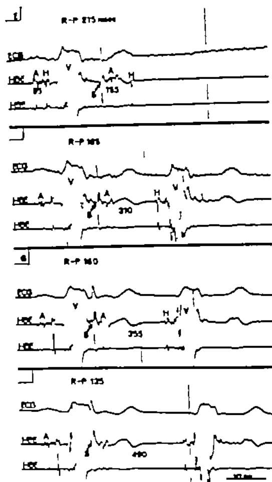


Fig. 3 Continuous tracing of Fig 2.

recovery of the His-Purkinje system

According to definition it is apparent that our cases satisfy the criteria for so-called supernormal conduction Equally apparent is the fact that this term obscures the physiological mechanism responsible for unexpected A V conduction. Our electrophysiological findings in man are in agreement with some of the concepts put forth by Moe and associates[3] in their extensive report on this subject. These investigators examined a number of electrocardiographic manifestations of supernormal conduction and eliminated supernormality as a factor in most if not all of the published reports. Alternative explanations for apparent supernormal A V conduction depend upon the relationship between the state of refractoriness of the A V nodal and His-Purkinje systems.

The phenomenon described in this report is the same as the phenomenon of "gap in A V conduction" which was described for the canine heart by Moe and associates.[14] Wit and associates[11] provided the electrophysiological explanation of this phenomenon in their more extensive studies in the human heart. These latter investigators also demonstrated that when the effective refractory period of the His Purkinje system is shortened by increasing the basic heart rate the "gap in A V conduction" can be abolished.

The results of the present study provide an electrophysiological explanation for one type of so-called supernormal A V conduction based on the relationship between the state of refractoriness of the A V nodal and His-Purkinje conduction systems.

Summary

The mechanism of one type of so-called supernormal A V conduction was elucidated in 11 subjects during premature atrial stimulation studies using His bundle electrogram recordings. At relatively long R P intervals atrial impulses failed to conduct to the ventricles and were blocked distal to the bundle of His. At shorter R P intervals A V conduction resumed. The more premature atrial impulses encountered greater A V nodal delay (longer A H interval) and arrived within the His Purkinje system after the latter was more completely repolarized. The electrophysiological mechanism for this type of so-called supernormal A V conduction is based on the relationship between the state of refractoriness of the A V nodal and His Purkinje conduction systems.

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Diagnosis of coarctation of the aorta by infrared thermography

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The successful application of infrared thermography to the diagnosis of many disease entities has opened new vistas in medicine. This new diagnostic capability has had a number of applications to vascular disease, including peripheral vascular disease, ischemic heart disease, and cerebrovascular disease,[1-8] but to our knowledge it has not been used in the study of coarctation of the aorta.

In coarctation of the aorta, blood reaches the lower part of the body through an extensive series of collateral arteries arising above the coarctation. Demonstration of the collateral circulation is indirect evidence of the presence of coarctation, but collateral vessels may not be sufficiently large and tortuous to be detectable on physical examination. Physical examination, especially in an infant suspected of having coarctation, may be misleading, resulting in both false-positive and false-negative impressions. Angiography and cardiac catheterization, while objective and definitive, carry a significant risk which is greatest in the younger age groups.

Infrared thermography possesses the capability of detecting increased collateral circulation years before the collateral vessels are sufficiently developed to result in a murmur or rib notching. Thermography is a safe, noninvasive study which may be repeated as many times as necessary without danger to the patient.

The purpose of this paper is threefold: (1) to demonstrate the thermographic display of vascular patterns in normal, healthy children between the ages of 4 and 11 years, (2) to demonstrate the thermographic display of vascular patterns in children with clinically diagnosed coarctation of the aorta, and (3) to suggest tentative working guidelines for the thermographic diagnosis of coarctation of the aorta.

Methods

The study population consisted of 6 children with unequivocal clinical evidence of coarctation of the aorta and 22 normal healthy children. The age ranges were 4 to 9 years for the disease population and 3 to 12 years for the control group.

Thermography is a pictorial mapping of the infrared energy patterns emitted by the skin. The emission of this radiant energy is a function of the absolute temperature of

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the skin While skin temperature is influenced by the metabolic rate of the body as well as by the environmental temperature variations in skin temperature from one point on its surface to another are a reflection of the heat transmitted to the skin surface by underlying structures such as organs and blood vessels. Heavily vascularized areas of the skin normally emit greater amounts of infrared energy than less vascular areas. In a thermal radiation scale ranging from black to white cooler areas of the skin appear as darker shades of gray while warmer areas are displayed as lighter gray By the use of a standard reference source a thermal gray scale the temperature of any given point on a thermogram may be determined

The instrument used was the Barnes-Bofors M 101 thermograph Studies were carried out in a draft free light-shielded thermostatically controlled room in which the temperature was maintained between 68° and 72 F Subjects were required to equilibrate for a minimum of 15 minutes. Swim trunks or underpants were worn These were rolled down to a level just above the pubic bone in order to ensure maximum exposure of the areas to be studied

Thermograms consisted of anterior posterior left and right lateral views of the neck and trunk A thermal gray scale was included in each thermogram to facilitate availability of precise temperature reference data A Delta T of 2° C was used in all subjects in some cases additional studies were performed at a Delta T of 1 C

Case histories

Case 1 This 6-year-old Caucasian boy was the product of a normal pregnancy and delivery At age 3 months a heart murmur was heard. At age 5 years diminished femoral pulses were noted and the diagnosis of coarctation of the aorta was made. Growth and development had been normal and the child was entirely asymptomatic.

The femoral pulses were very faint compared to the brisk brachial pulses. Blood pressure was 144/80 in the right arm and 138/88 in the left arm. Blood pressures were not obtainable in the lower extremities. There was a Grade 3/6 systolic and diastolic continuous murmur just medial to the left scapula. This murmur was well heard at the second left interspace anteriorly There was no ejection sound and no cardiac murmur

Chest X rays showed rib notching from the fourth to the sixth ribs bilaterally and a slight prominence of the left ventricle. The electrocardiogram (ECG) was within normal limits. A thoracic aortogram showed a markedly narrowed aorta just distal to the left subclavian artery Both internal mammary arteries were enlarged.

Thermograms in the posterior projection showed increased radiations directly overlying the scapulae and the infrascapular region bilaterally (Fig. 1 panel *1*) This pattern was mildly asymmetric, with slightly increased temperatures over the right scapula. Thermal radiations conformed to a pattern suggestive of an Indian arrowhead. Below the sixth thoracic vertebra, radiations over the spinal column were significantly decreased Thermograms in the anterior projection showed a bilateral increase of abdominal vascularity above the umbilicus (Fig 2 panel *1*). Supraclavicular radiations were increased.

Lateral thermograms revealed a symmetrical increase in thermal radiations over the lateral intercostal spaces. The area of increased radiations was more extensive on the right lateral projection.

Case 2 This 10-year-old Caucasian boy was found to have a heart murmur mild hypertension, and diminished femoral pulses at 5 years of age. His growth and development had been normal and he was asymptomatic except for easy fatigability of the lower extremities and frequent epistaxis.

Radial pulses were brisk and symmetrical. Femoral pulses were weak and delayed. Blood pressure in both arms was 160/105 pressures were not obtainable in the lower extremities. A high-frequency long, almost continuous murmur was heard over the vertebral column between the scapulae as well as over the left internal mammary artery There were prominent carotid and subclavian systolic bruits and soft murmurs in both axillae. There was a short mid systolic murmur in the second right interspace. Neither an ejection sound nor a diastolic murmur was heard.

The ECG was within normal limits. The chest X ray showed a normal heart and great vessels but notching of the fourth left rib was seen.

Thermograms in the posterior projection showed increased thermal radiations in an arrowhead pattern below and overlying the scapulae (Fig 1 panel *2*) Radiations were slightly increased over the right scapula and radiations were markedly decreased over the vertebral column below the sixth thoracic vertebra Lumbosacral radiations were not visualized the right posterior cervical region showed increased radiations. Anterior thermograms showed two well developed vascular channels running in an oblique direction across the upper abdominal quadrants (Fig. 2 panel *2*) Lateral thermograms were not included in the initial study of this child.

Case 3 This 4-year-old asymptomatic Caucasian boy was referred for evaluation of a cardiac murmur He was the product of a pregnancy complicated by scarlet fever in the second month and by threatened abortion in the fourth month His birth was uncomplicated and he passed all of his developmental milestones adequately At age 1½ a heart murmur was heard on a routine examination. He had not had easy fatigability epistaxis, headache, or tachycardia. His sister had cerebral palsy and also had had a patent ductus arteriosus surgically closed

Brachial and carotid pulses were normal. Femoral pulses were faint and slightly delayed. Blood pres-

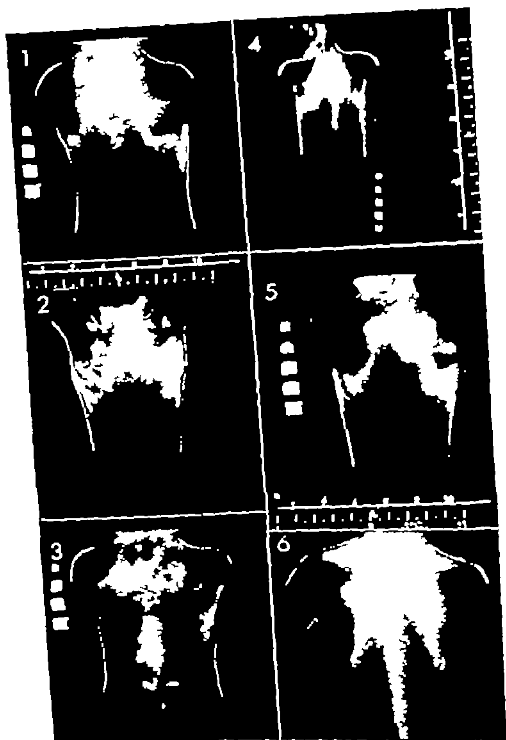


Fig. 1 Thermograms of children with coarctation of the aorta, posterior projection. Cool regions are thermographically dark gray or black, warmer areas are light gray or white. Skin overlying collateral vessels is warmer than surrounding regions and appears as a light gray-white pattern suggestive of an Indian arrowhead. The base of the neck forms the point of the arrow; the sides of the arrow flare out over both scapulae.

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Radial pulses were brisk and symmetrical. Femoral pulses were weak and delayed. Blood pressure in both arms was 160/105; pressures were not obtainable in the lower extremities. A high-frequency, long, almost continuous murmur was heard over the vertebral column between the scapulae as well as over the left internal mammary artery. There were prominent carotid and subclavian systolic bruits and soft murmurs in both axillae. There was a short midsystolic murmur in the second right interspace. Neither an ejection sound nor a diastolic murmur was heard.

The ECG was within normal limits. The chest X ray showed a normal heart and great vessels but notching of the fourth left rib was seen.

Thermograms in the posterior projection showed increased thermal radiations in an arrowhead pattern below and overlying the scapulae (Fig. 1, panel 2). Radiations were slightly increased over the right scapula and radiations were markedly decreased over the vertebral column below the sixth thoracic vertebra. Lumbosacral radiations were not visualized; the right posterior cervical region showed increased radiations. Anterior thermograms showed two well-developed vascular channels running in an oblique direction across the upper abdominal quadrants (Fig. 2, panel 2). Lateral thermograms were not included in the initial study of this child.

Case 3. This 4-year-old asymptomatic Caucasian boy was referred for evaluation of a cardiac murmur. He was the product of a pregnancy complicated by scarlet fever in the second month and by threatened abortion in the fourth month. His birth was uncomplicated, and he passed all of his developmental milestones adequately. At age 1½ a heart murmur was heard on routine examination. He had not had easy fatigability, epistaxis, headache, or tachycardia. His sister had cerebral palsy and also had had a patent ductus arteriosus surgically closed.

Brachial and carotid pulses were normal. Femoral pulses were faint and slightly delayed. Blood pres-

sure in both upper extremities was 120/80. Arterial systolic murmurs were heard above the clavicles and a venous hum was present on the right. A Grade 2/6 pure systolic murmur was heard over the vertebral column between the scapulae. An aortic ejection sound was heard at the apex.

The ECG exhibited a classic Type B Wolff-Parkinson-White tracing. An X ray of the chest showed a prominent left subclavian artery and conspicuous dilatation of the descending thoracic aorta. Subtle notching of the sixth and seventh posterior ribs on the left and of the sixth and eighth posterior ribs on the right was seen.

Thermograms in the posterior projection showed increased radiations overlying the scapulae, somewhat more marked on the left (Fig. 1, panel 3). Increased cervical warmth extended to the level of the first thoracic vertebra. The lumbosacral area was visualized. Anterior thermograms showed an extension of increased cervical radiations to the infraclavicular region (Fig. 2, panel 3). There was an increase in radiations in both upper abdominal quadrants, but specific vessels could not be delineated. Lateral thermograms were symmetrical except for subtle increase in radiations in the region of the left axilla.

Case 4. An 8-year-old Caucasian girl, a twin, born at another hospital, had developed congestive heart failure shortly after birth. The diagnosis of coarctation of the aorta was made at that time, and she was treated with digitalis. She remained in the hospital for 2½ months and continued on digitalis for 8 months. She was first seen at Georgetown University Hospital when she was 21 months old, at which time blood pressure in both arms was 130/85. Her subsequent course was favorable, and she had no significant illnesses. Her only complaints were mild fatigue of the lower extremities and spontaneous nosebleeds.

Femoral pulses were small and delayed. Pedal pulses were not palpable. Blood pressure in both arms was 150/85. There was a long systolic murmur over the vertebral column between the scapulae. Murmurs were widely distributed over the thorax, especially in the left axilla. An aortic ejection sound was heard, but there was no distinct systolic or diastolic murmur across the aortic valve.

The ECG showed voltage criteria of left ventricular hypertrophy (S_{V1} 30 mm., R_{V5} 25 mm.) but no S-T or T wave changes. Chest X ray showed no cardiac enlargement or aortic prominence. There was no rib notching.

Thermograms in the posterior projection showed increased radiations below and overlying both scapulae (Fig. 1, panel 4) particularly on the left side. Below the tenth thoracic vertebra thermal radiations were sharply decreased. The lumbosacral region was only faintly visualized. Anterior thermograms revealed cervical warmth extending well below the clavicles (Fig. 2, panel 4). The upper abdominal quadrants showed a generalized increase in warmth. Several small, discrete areas of increased temperature were present in the left upper quadrant, overlying the superior epigastric artery. Lateral thermograms showed decreased radiations in the supraglottal regions bilaterally. The left lateral intercostal region was warmer than the right.

Case 5. This 5-year-old girl was found to have



Fig. 3. X ray of Patient 5 showing collateral rib notching, right side.

systolic heart murmur and absent femoral pulses immediately after birth. She had been a full-term baby of a normal pregnancy. At age 6 months blood pressure in the right arm was 210/140 and in the left arm 160/120. No blood pressure was obtained in either leg. Her growth and development progressed normally and she was asymptomatic.

At 5 years blood pressure in the right arm was 158/90 in the left arm 108 systolic by palpation. There was a suggestion of palpable collateral circulation in the right chest posteriorly. Auscultation of the interscapular area revealed a long systolic murmur bilaterally which spilled over into diastole on the left.

There was a systolic thrill in the suprasternal notch and a rather slow rate of rise of the carotid pulse. The left brachial pulse was diminished and delayed in comparison to the right brachial pulse. Femoral pulses were delayed and barely palpable. An aortic ejection sound and third and fourth heart sounds were present. A Grade 3 aortic ejection murmur was heard but no diastolic murmur was detectable. These findings indicated that the area of coarctation partially involved the left subclavian artery.

The ECG was within normal limits. Chest X rays showed notching of the fifth and eighth ribs on the right but none on the left (Fig. 3). The aortic contour appeared normal.

Thermograms in the posterior projection demonstrated increased radiations overlying the right scapula (Fig. 1, panel 5 and Fig. 4). The skin overlying the left scapula was cool. Both infrascapular areas were warm, contributing to the formation of an asymmetric arrowhead pattern which was cooler on the left side. Radiations over the vertebral column were decreased below the sixth thoracic vertebra. Lumbosacral radiations were only faintly perceptible.

Thermograms in the anterior projection (Fig. 2, panel 5 and Fig. 4) showed an increase in cervical temperatures as well as an enlargement of the area of cervical warmth. A prominent vascular channel was seen in the right upper abdominal quadrant,

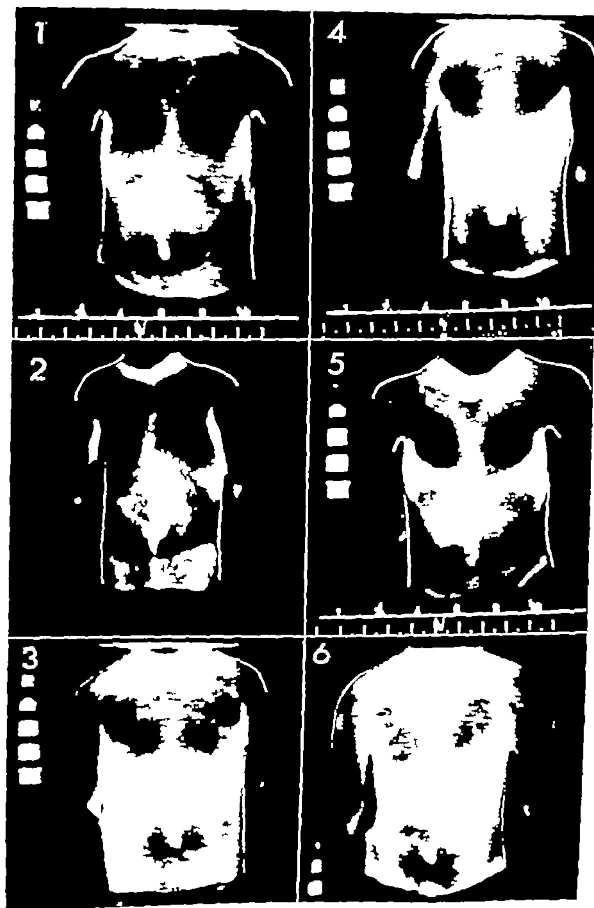


Fig 2 Thermograms of children with coarctation of the aorta anterior projection. The umbilicus is warm. Discrete areas of increased thermal radiations (Patients 1 2 and 5) represent dilated superior epigastric arteries.

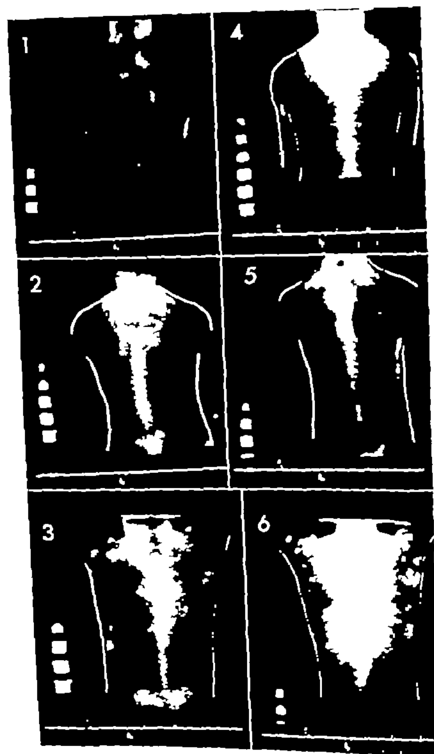


Fig. 5. Thermograms of 6 representative control subjects, posterior projection. Subjects 1, 2, 3, 4, and 5 show increased thermal radiations in a "Y"-shaped pattern. Highest temperatures occur over the vertebral column, fanning out in the interscapular region. Subject 6 shows a more diffuse distribution of temperatures, seen in 3 of 22 subjects.

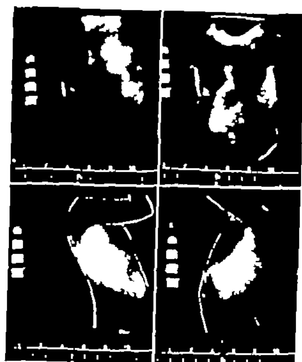


Fig. 4 Composite thermograms, Patient 5 Right lateral thermogram shows increased thermal radiations. Posterior thermogram shows asymmetric arrowhead pattern with greater collateral development on the right side.

extending downward in an oblique direction to a point lateral to the umbilicus.

Lateral thermograms showed decreased radiations in the supragluteal regions bilaterally (Fig 4) The right lateral intercostal area showed an increase in warmth which extended from the axilla to the level of the seventh rib in contrast to the cooler left lateral view

Case 6 This was a 9-year-old Caucasian boy in whom absent femoral pulses were detected on a routine examination at age 6 months. His gestation and birth had been normal and he developed into an active, asymptomatic young boy with none of the minor symptoms of coarctation such as leg fatigue epistaxis, or headache.

Radial pulses were equal. Femoral pulses were reduced and delayed. Blood pressure was 110/80 in both arms. Intercostal arterial collateral pulses were palpable at the angles of the scapulae. Soft murmurs were heard over the subclavian and carotid arteries, the left sternal edge, and the interscapular area. There was no ejection sound and no diastolic murmur

The ECG was within normal limits. X rays of the chest showed a heart of normal size. Although rib notching had not been present at age 5 mild notching of th right sixth nd seventh ribs was seen at age 9

Thermograms in the posterior projection showed a moderate increase in radiations overlying the scapulae (Fig 1 panel 6) Increased radiations were seen beneath both scapulae. A localized, somewhat discrete area of warmth was observed to the left of the fourth and fifth thoracic vertebrae. The vertebral column, including the lumbosacral region, was visualized thermographically although radiations were reduced in intensity

Anterior thermograms of the thorax showed a generalized diffuse increase in radiations (Fig. 2, panel 6) Small discrete areas of increased thermal radiations were seen in both upper quadrants as well as in the left lower quadrant. The root of the neck showed an increase in infrared energy emission as well as an increase in actual area of emission, which extended to the infraclavicular region. A vascular channel was clearly delineated immediately lateral to the suprasternal notch.

Results

Thermographic studies were performed on 22 healthy children ranging in age from 4 to 11 years. Thermograms in the posterior projection were characterized by two general patterns. The first pattern seen in 19 control subjects was one of increased radiations conforming to a Y'-shaped configuration (Fig 5 panels 1 2 3 4 and 5) The region directly overlying the vertebral column was the area of greatest warmth The cervical region from the hairline to the level of the seventh cervical vertebra had temperatures which were 2° C higher than the remainder of the spine. Below this level temperatures were uniform appearing as a narrow gray white segment overlying the vertebral column. In normal controls this segment widens in two places the interscapular and lumbosacral regions. The interscapular widening results in the Y pattern seen in 92 per cent of normal control subjects. The skin overlying the scapulae and the infrascapular region was cooler than that of the vertebral column in 86 per cent of control subjects.

The second pattern seen in normal subjects was a modification of the Y' pattern (Fig 5 panel 6) Although these subjects showed the same increase in thermal radiations over the vertebral column there was a more diffuse homogeneous distribution of warmth peripheral to the spine. This pattern was seen in 3 of the control subjects.

Anterior thermograms of normal children were symmetrical in 95 per cent of the subjects (Fig 6) The anterior projection demonstrated warmth over the cervical region. Below the clavicle radiations were decreased over the pectoralis major with maintenance of moderate warmth over the midline. This warmth continued down

ward over the linea alba, ending at the umbilicus. The periumbilical region was cooler than other areas of the abdomen and approximated the temperatures obtained over the pectoral regions. The umbilicus was invariably warm No control subject demonstrated thermographic patterns indicative of increased thoracic or abdominal vascularity

Thermograms in the lateral projection were symmetrical in the distribution of warmth Axillary and infra axillary areas were slightly warmer bilaterally radiations decreased slightly over successively lower ribs, but in general showed a diffuse homogeneous distribution bilaterally

In the six children with coarctation of the aorta, thermograms in the posterior projection showed a distribution of increased radiations conforming to an Indian arrowhead pattern (Fig 1) The base of the neck formed the point of the arrow which then flared out over both warm scapular areas. This pattern demonstrated a varying degree of asymmetry in all but one case (Fig 1 panel *6*) Asymmetry involved variations in temperature as well as in the extent of area involved All 6 cases of coarctation showed increased radiations over the scapulae. Five subjects had an increase of infrascapular warmth Four of the 6 subjects had a marked decrease in radiations overlying the vertebral column below the thoracic level. In subjects No 3 and No. 6 the lumbosacral region was visualized easily in subjects No. 1 4, and 5 it was faintly visible, and in subject No 2 it could not be visualized at all

Anterior projections in coarctation subjects generally showed a moderate diffuse increase in radiations in both thorax and abdomen. The normally cool pectoral and periumbilical regions were reduced in area. In three subjects (Fig 2 panels *1 2* and *5*) there were strikingly accentuated localized areas of increased thermal radiations over the upper abdominal quadrants.

The cervical region demonstrated increased temperatures compared to temperatures over the manubrium. Three coarctation cases showed extension of cervical warmth below the clavicle (Fig 2, panels *4 5* and *6*)

Lateral thermograms in 5 diseased subjects showed asymmetry in degree and in

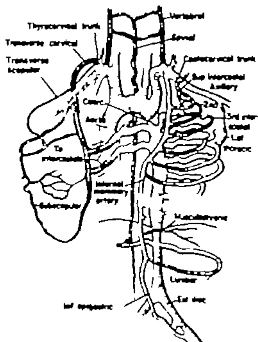


Fig 7 Diagram of collateral circulation in coarctation of the aorta. Details on the left demonstrate arteries of the left anterior thorax, abdominal wall, ad left lower extremity The right side demonstrates collateral flow in the parascapular arteries and its large communications t the intercostal arteries. The details for the left side are pplicable to the right side as well. (Revision by Edwards of the original diagram published in Mayo Clinic Proceedings 23 333 1948 by Edward, J E., et al. Reproduced with permission.)

area of radiations the lateral projection of greater warmth corresponded to the side of greater warmth on the posterior projection (Fig 4) Decreased radiations over the gluteal regions extended in an anterolateral direction to the iliac crests.

Discussion

The thermographic patterns of the 6 children with coarctation of the aorta are distinctly different from those of the control subjects. Analysis of these thermograms in the light of the pathologic anatomy and physiology of coarctation reveals that thermographic patterns reflect the compensatory vascular adjustments which have developed in response to the lesion.

When the area of coarctation is distal to the ductus arteriosus, collateral vascular channels develop during fetal life. The subclavian arteries and their branches constitute the important sources of collateral

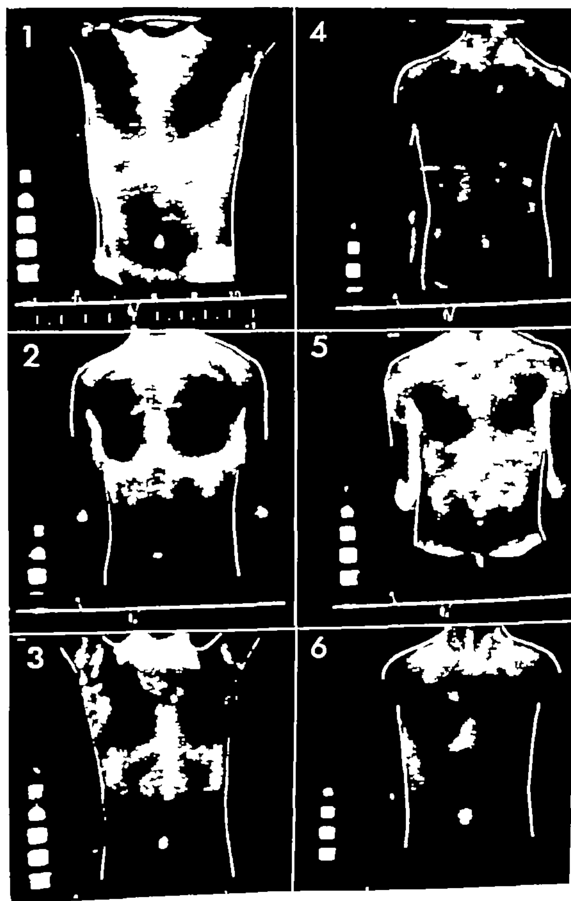


Fig. 6. Thermograms of 6 normal control subjects, anterior projection. Pectoral and periumbilical regions are cool. The neck is warm, as is the region immediately overlying the sternum. The umbilicus is warm.

in which the diagnosis is not clinically apparent.

Conclusion

Infrared thermography was applied to 6 children with clinically diagnosed coarctation of the aorta and to 22 normal children in the same age group. Thermograms of the diseased subject group demonstrated distinctively different patterns of thermal radiations from those of the normal control subjects.

Thermograms of patients with coarctation revealed heat emission patterns of collateral arterial blood flow that are indirect evidence of the underlying disorder.

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flow by means of which the area of aortic constriction is bypassed (Fig 7)

The transverse cervical and transverse scapular branches of the thyrocervical trunk form many anastomotic channels around the scapulae and contribute significant blood flow to the lower aorta via the intercostal arteries. Thermographically this route of collateral flow is best demonstrated by posterior thermograms.

In examining posterior thermograms of 6 cases of coarctation it is possible to correlate thermal radiations with the vascular anatomy discussed above Within the general configuration of the arrowhead pattern distinct vascular channels may be seen in some cases (Fig 1 panel *2*) Case No 2 reveals a prominent vascular channel the circumflex scapular branch of the axillary artery running in an almost horizontal direction across the superior aspect of the right scapula and giving off a branch to the teres minor

The parascapular arteries are a major source of blood flow to the intercostal arteries.[4] The dilated intercostal vessels follow the oblique direction of the posterior ribs and contribute to the development of the arrowhead pattern seen in accompanying thermograms. All six cases of coarctation have prominent areas of increased radiations representative of vascular channels. Most of these areas conform in location and distribution to vessels of the parascapular group superimposed upon and anastomosing with the underlying posterior intercostal vessels.

Although all but one posterior thermogram showed some degree of asymmetry Case No 5 demonstrated asymmetry of marked degree with highly developed collateral flow on the right side and relatively little vascular development on the left These thermographic findings correlated perfectly with the clinical evidence that the coarctation of the aorta actually involved the left subclavian artery Accordingly the dominant collateral circulation was through the right subclavian artery This asymmetry of collateral vascular development was conspicuous on the posterior thermogram

While normal subjects display a cervical skin temperature which is moderately higher than that of the thorax it is confined to a relatively restricted area. The coarctation subjects show a pronounced temperature elevation which extends over a diffuse area. In 5 of the diseased subjects cervical warmth extended well below the clavicles. These increased thermal radiations in the posterior cervical region reflect increased flow through neck vessels, all of which are in the high pressure area proximal to the coarctation Many arterial branches from the thyrocervical trunk and external carotid system spread over the posterior cervical region and contribute to the increased thermal radiations.

In a similar manner the generalized increase in temperatures over the anterior thorax and abdomen reflects collateral vascular development via the internal mammary arteries. This diffuse warmth seen in diseased subjects is in distinct contrast to that of normal control subjects in whom anterior thorax and periumbilical regions are relatively cool except for the sternal region where small perforating branches of the internal mammary arteries account for moderate temperature elevations.

The generalized diffuse warmth of the abdominal quadrants in the patients with coarctation is a reflection of extensive collateral flow between the internal mammary arteries the inferior epigastric arteries and their branches. In these patients (Fig 2 panels *1* *2* and *5*) it was possible to delineate individual dilated arteries, probably the superior epigastric arteries.

Lateral thermograms of coarctation subjects are of interest in that they give corroborative evidence of asymmetry of thermal radiations demonstrated on posterior and anterior thermograms. In the present study lateral thermograms have not provided any information which was not apparent in anterior and posterior thermograms.

The patterns of collateral flow exhibited in these cases of coarctation of the aorta have been limited to those patients with unequivocal clinical evidence of the disease ranging in age from 4 to 9 years old Whether similar findings occur in infancy or in less obvious cases of coarctation is not yet established The value of thermography as a clinical diagnostic tool in this disease will naturally depend on how well it delineates the collateral blood flow in cases

Table I *Edrophonium effect on atrial flutter*

Case	Digitalis status	Control rate	Edrophonium effect
1	0	2 1 Block	0
2	0	1 1 Response	0
3	0	Variable block	0
4	0	2 1 Block	0
5	0	2 1 Block	0
6	0	2 1 Block	0
7	0	2 1 Block	0
8	0	2 1 Block	0
9	+	2 1 Block	3 1 Block
10	+	2 1 Block	10-sec. Asystole
11	+	2 1 Block	4 1 Block
12	+	2 1 Block	3 1 Block
13	+	2 1 Block	3 1 Block

Table II *Atrial tachycardia*

Case	Digitalis status	Control rate	Edrophonium effect	Time when maximum effect was seen (min.)
1	+	190	Atrial fibrillation	3
2	+	120	2 1 Block	2
3	+	122	Sinus tachycardia	2
4	+	188	3 1 Block	10
5	+	158	0	—
6	+	140	0	—
7	+	140	0	—
8	+	143	0	—
9	+	150	2 1 Block	1
10	+	125	Sinus rhythm (75)	1
11	+	2 1 Block	12 1 Block	3
12	+	2 1 Block	27 1 Block	3
13	+	250 (2 1 Block)	4 1 18 1 9 1 4 1 Block	2
14	0	215	0	—
15	0	180	0	—
16	0	170	0	—
17	0	170	0	—
18	0	212	0	—
19	0	132	Sinus rhythm (81)	1
20	0	143	0	—
21	0	125	0	—
22	0	214	0	—
23	0	170	0	—
24	0	240 (2 1 Block)	0	—

A positive response denotes either definite slowing of the atrial rate in sinus tachycardia or sinus rhythm conversion of atrial tachycardia to normal sinus rhythm or to atrial tachycardia with block, or an increase in atrioventricular block with slowing of the ventricular response in atrial flutter or atrial fibrillation. The effects of edrophonium were usually evident within 1 to 3 minutes after its intravenous administration and subsided within 15 minutes.

Normal sinus rhythm. Of the 18 patients, 9 were taking digitalis and 8 were not, and the status of 1 patient was unknown. Cardiac slowing occurred in 8 of the patients on digitalis. A paradoxic increase of 30 beats was observed in the one other patient on digitalis. Three of the nondigitalis pa

Use of edrophonium (Tensilon) in the evaluation of cardiac arrhythmias

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Carotid sinus massage and ocular compression are useful vagotonic maneuvers in the evaluation of supraventricular tachycardias. Not infrequently, these maneuvers are ineffective in producing a vagal cardiodepressant effect. Neostigmine, a parasympathomimetic agent, has been used in the past in the evaluation and treatment of supraventricular tachycardias.[1] However, the sustained cholinergic action has been associated with alarming reactions.[2]

Edrophonium chloride (Tensilon), a quaternary ammonium compound which had been used in the diagnosis of myasthenia gravis, has recently been found to be helpful in evaluating supraventricular tachycardias.[3-6] Its transient cholinergic effect virtually eliminates serious complications. In addition, one group has even found edrophonium to be valuable in the detection of early digitalis toxicity.[4]

This report presents our experience with the use of edrophonium in the evaluation of various arrhythmias.

Methods

One hundred and three patients were studied. There were 21 cases of sinus tachycardia, 27 cases of atrial fibrillation, 24 cases of supraventricular tachycardia, 13 cases of atrial flutter, and 18 cases of normal sinus rhythm. For each patient, a complete electrocardiogram was recorded and 10 mg. of edrophonium was administered in a single rapid intravenous injection. One lead of the electrocardiogram, usually Lead II, was recorded from 5 minutes before until 20 minutes after the injection of edrophonium. The patients were observed for the occurrence of any side effects or complications after the administration of the drug. Atropine and emergency equipment for cardiac resuscitation were constantly available. The statistical significance of the differences (P values) between the control values and the edrophonium values was calculated with the Student t test.

Results

The basic clinical data on the 103 patients to whom edrophonium was administered are presented in Tables I-V. The average values of the cardiac rate before and after edrophonium are listed in Table VI. Edrophonium was administered 103 times to 84 patients, and a positive response to edrophonium was noted on 71 occasions.

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Table V Normal sinus rhythm

Case	*Digitalis status*	*Control rate*	*Edrophonium effect*	*Time when maximum effect was seen (min.)*
1.	+	100	94	2
2.	+	97	127	5
3.	+	90	78	7
4.	+	87	82	1
5	+	94	75	3
6.	+	100	68	3
7	+	100	68	5
8.	+	83	86	1
9	+	86	72	
10.	0	100	99	5
11.	0	97	97	—
12.	0	65	65	—
13.	0	97	80	2
14.	0	82	67	10
15.	0	93	78	10
16.	0	77	77	—
17	0	90	85	2
18.	?	100	80	2

Table VI Average values of the cardiac rate before and after edrophonium administration

	Normal sinus rhythm, Digitalis group	*Normal sinus rhythm, Nondigitalis group*	*Sinus tachycardia, Digitalis group*	*Sinus tachycardia, Nondigitalis group*	*Atrial fibrillation, Digitalis group*	*Atrial fibrillation Nondigitalis group*
Control rate	94	89	124	124	112	132
Edrophonium rate	83	81	95	110	79	115
p Value	N.S.	N.S.	<0.05	N.S.	<0.01	N.S.

tients showed no change in rate with edrophonium whereas the other 5 patients demonstrated a transient slowing. The decline in the cardiac rate was not statistically significant in the digitalis and nondigitalis groups.

Sinus tachycardia In 18 of the 21 patients with sinus tachycardia the administration of edrophonium gradually and transiently reduced the cardiac rate. Two of the patients did not respond and one patient showed a paradoxic increase in the cardiac rate. This patient had previously demonstrated this unusual response when she was in normal sinus rhythm (Fig 1) A significant decline in the cardiac rate occurred in the group taking digitalis ($p < 0.05$) whereas the nondigitalis group showed no significant change. When these two groups were compared with each other no statistical difference was observed

Atrial flutter Eight patients who were not taking digitalis showed no change in the cardiac rate when edrophonium was administered However the 5 patients on digitalis responded to edrophonium with an increase in atrioventricular block (Fig 2) One of these patients developed a 10-second period of asystole with only atrial flutter waves on the electrocardiogram. This patient had previously been in atrial fibrillation but with large doses of digitalis developed atrial flutter With the intravenous administration of 1 mg of atropine, atrial fibrillation with a rapid ventricular response of 160 per minute was observed.[4]

Atrial fibrillation. All but 1 of the 27 patients demonstrated with administration

Table III. Edrophonium effect on atrial fibrillation

Case	Digitalis status	Control rate	Edrophonium effect	Time when maximum effect was seen (min.)
1	+	93	53	3
2	+	101	81	2
3	+	101	60	2
4	+	91	73	3
5	+	86	58	2
6	+	101	58	2
7	+	115	57	2
8	+	156	107	3
9	+	141	109	1
10	+	81	61	½
11	+	158	85	1½
12	+	160	103	2
13	+	83	64	2
14	+	74	46	2
15	+	120	107	1
16	+	150	100	2
17	+	80	55	3
18	+	90	60	2
19	+	110	86	2½
20	+	97	59	1
21	+	187	167	2
22	+	88	75	2
23	0	143	123	2
24	0	117	77	½
25	0	131	105	2
26	0	140	130	2
27	0	130	130	—

Table IV. Edrophonium effect on sinus tachycardia

Case	Digitalis status	Control rate	Edrophonium effect	Time when maximum effect was seen (min.)
1	+	133	105	2
2	+	111	83	2
3	+	111	57	2
4	+	115	83	5
5	+	136	130	2
6	+	135	110	2
7	0	107	127	2
8	0	107	102	4
9	0	120	111	2
10	0	105	100	10
11	0	163	145	1
12	0	169	75	2
13	0	115	107	1
14	0	125	117	1
15	0	105	98	7
16	?	110	110	—
17	?	120	110	2
18	?	125	125	—
19	?	120	100	2
20	?	110	95	2
21	?	120	115	1

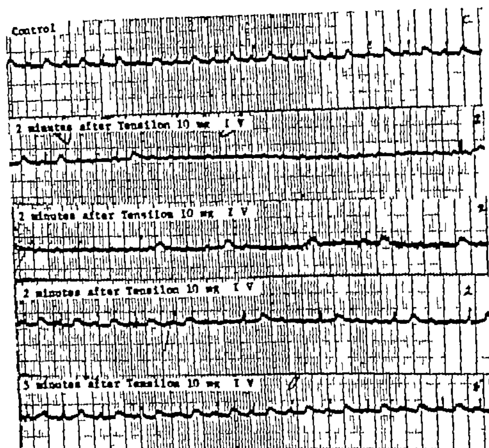


Fig. 2 I patient with atrial flutter edrophonium (Tensilon) produced a striking increase i the atrioventricular block.

reverted to atrial fibrillation and 1 developed sinu hythm Four additional patients initially showed atrial tachycardia with block on thei electrocardiograms. Edrophonium produced a transient 12 1 block in one subject, a 27 1 block in a second subject, and an 18 1 block in third subject. These three ndividuals were on digitalis. The one subject who was not on d gitalis showed no response with edrophonium

Discussion

Edrophon um is a useful vagotonic drug in the differentiation of supraventricular tachycardias. It increased atrioventricular block n atrial fibrillation, and it produced a transient slowing n sinus tachycardia. If the patient was taking digitalis, then edrophon um increased the atrioventricular block n atrial flutter However the non digitalized patient with atrial flutter did not respond to edrophonium administration.

A sinus mechanism was restored in only 2 of the 10 digitalized patients with atrial tachycardia, while 4 of the subjects developed atrial tachycardia with A V block. Indeed edrophonium appears to have considerable effect on patients with atrial flutter or tachycardia if they are on digitalis. Furthermore, the nature and severity of this effect may be alarming Accordingly it would appear to be prudent not to give edrophonium to patients with atrial flutter or tachycardia who are taking digitalis.

Only one of the nondigitalized patients with atrial tachycardia converted to sinus rhythm This was a surprisingly poor result and differs from the good results reported by Moss and Aledort.[3] They administered edrophonium to 12 patients with atrial tachycardia, and successful conversion to sinus rhythm was obtained on 6 occasions.

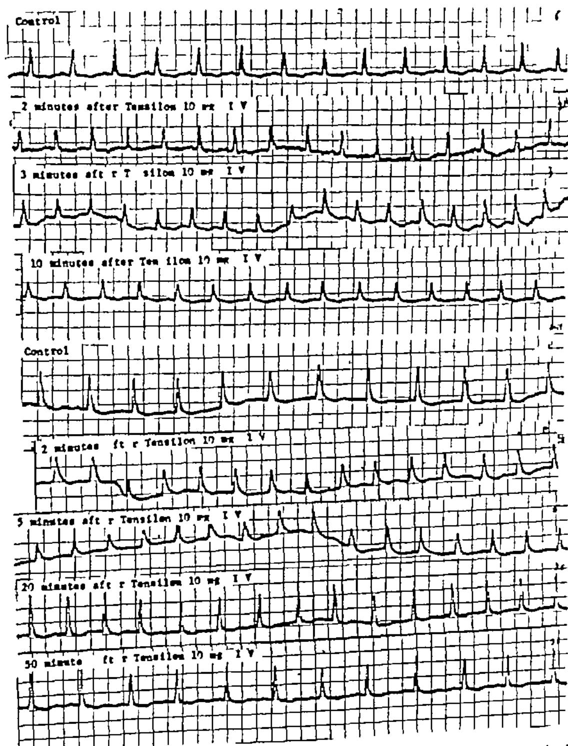


Fig. 1 Edrophonium (Tensilon) produced a transient increase in the sinus rate on two occasions in the same patient.

of edrophonium a decrease in the ventricular response. In 7 patients with rapid supraventricular tachycardias the diagnosis of atrial fibrillation was confirmed with the administration of edrophonium after which the atrioventricular block increased and the fibrillatory waves became more evident. A very significant decline in the cardiac rate occurred in the group taking digitalis ($p < 0.01$) whereas the nondigitalis group showed no significant change.

Atrial tachycardia. Ten patients were not on digitalis. Nine showed no response with edrophonium and one reverted to a persistent sinus rhythm. Of the 10 patients taking digitalis, without evident A-V block, 3 developed transient atrial tachycardia with block, 4 did not respond, 1 demonstrated a transient sinus tachycardia, 1

demonstrated occasional ventricular premature beats prior to the infusion of edrophonium. A transient increased number of ventricular premature beats developed after edrophonium. Two additional patients, one in sinus rhythm and one in atrial fibrillation, had no ventricular premature beats on the control electrocardiogram. Edrophonium produced frequent ventricular premature beats in both of these patients (Fig. 3). The administration of edrophonium led to a decrease in the cardiac rate in these 4 patients, which presumably favored the emergence of a subsidiary ventricular pacemaker. In addition, all of the patients had received an excess of digitalis.

One patient in sinus rhythm responded to edrophonium with a transient increase in the cardiac rate. The explanation for this paradoxic effect is unknown, however, it serves to alert the physician to a potential complication of edrophonium administration.

Summary

Edrophonium has been reported to be valuable in the differentiation of supraventricular tachycardia. To evaluate the clinical usefulness of edrophonium, 10 mg of it was given intravenously to 103 patients with various arrhythmias. The electrocardiogram was then monitored for 30 minutes after administration of the drug. Edrophonium had no effect in 13 patients with atrial tachycardia, 3 developed atrial tachycardia with block, 3 showed a decrease in rate, and 1 developed atrial fibrillation. Twenty-six of the twenty-seven patients with atrial fibrillation showed a decrease in the ventricular response. Eight patients with atrial flutter had no response, 1 showed transient asystole, and 4 increased the block. Of the 21 cases of sinus tachycardia, 18 slowed, 2 showed no response, and in 1 the rate increased.

The maximum effect was seen within 2 to 3 minutes. By 15 to 20 minutes the baseline electrocardiogram was again observed. Side effects included abdominal discomfort, nausea, blurring of vision, lacrimation, and leg cramps.

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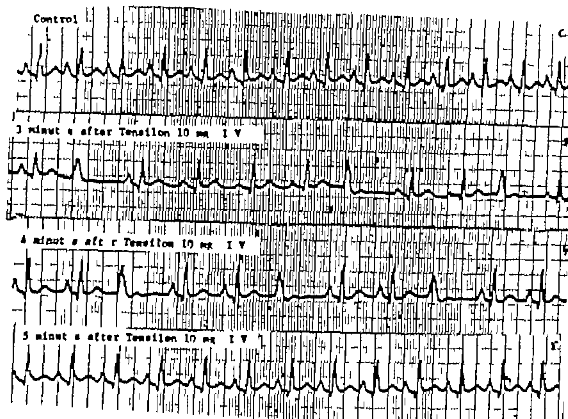


Fig 3 Administration of edrophonium (Tensilon) led to the production of frequent ventricular premature beats.

The discordant results of the studies are at the moment unexplainable.

Another potential use for edrophonium is in the evaluation of the functioning of implanted demand pacemakers. When the patient is in sinus rhythm it may be difficult to ascertain if the pacemaker is functioning without the use of an external magnet or carotid sinus pressure However the magnet may not be available and carotid massage may not produce an adequate decrease in the cardiac rate or may be contraindicated Edrophonium which can slow the rate will allow the demand pacemaker to take over as the dominant pacemaker

Mode of action Edrophonium a quaternary ammonium compound acts by inhibiting cholinesterase. Since edrophonium is hydrolyzed by cholinesterase it competes with acetylcholine for this enzyme. Edrophonium acts on the cardiac conduction system by potentiating the effect of acetylcholine normally released by the vagi Administration of the drug may be expected to produce sinus slowing to increase atrioventricular block and to convert ectopic atrial tachycardia to normal sinus rhythm.

Since the duration of action of edrophonium is very brief it is important that the drug be given as a rapid intravenous injection Ten milligrams is the dose that is usually employed However in a digitalized patient, edrophonium may potentiate the vagal effects of digitalis. Therefore, 5 to 7 mg should probably be given This potentiation between digitalis and edrophonium was well demonstrated in the present study Three of the patients had received an excess of digitalis as manifested by the recent appearance of atrial tachycardia with block and atrial flutter Edrophonium produced in these patients an alarming increase in the atrioventricular block. Fortunately this arrhythmia was transient, and serious complications did not ensue. It would appear to be prudent during the administration of edrophonium to have constant electrocardiographic monitoring as well as adequate facilities for cardiopulmonary resuscitation

Transient side effects were common in most of the patients and consisted of abdominal cramps, nausea, salivation and lacrimation Two of the patients, one in atrial fibrillation and one in sinus rhythm

Table I. Criteria for diagnosis of myopericarditis

ECG manifestation		*Symptoms*
a. ST-T or T wave changes, or b. Low QRS voltage or c. A-V conduction defects, or d. Intraventricular conduction defects	*Plus 2 or more symptoms*	1. Precordial left-sided chest pain 2. Signs and symptoms of congestive heart failure 3. Cardiomegaly 4. Fever 5. Pericardial friction rub

We identified neutralizing antibody titers to Coxsackie B antigens, types 2, 3, 4 and 5 using a microtiter method described by Lamb and associates.[11] These antigens were selected because they represented the serotypes most commonly encountered in our laboratory and because they are most frequently associated with myopericarditis.[12]

Virus isolation was attempted in 48 of the 63 patients. Rectal swabs and throat swabs were obtained and pericardial fluid was also cultured whenever it was available. All specimens were processed and inoculated into rhesus monkey kidney, Hep-2, and human diploid fibroblast monolayer cell cultures, using standard methods.[13]

Criteria for diagnosis of myopericarditis. The diagnostic criteria are summarized in Table I. We realize that these criteria do not distinguish whether the individual disease predominantly involved the myocardium or the pericardium or both; for example, it is probable that nearly all patients with clinically diagnosed pericarditis have some degree of subepicardial myocarditis. These criteria were chosen, however, because they represented the most uniform set of findings used by the physicians in caring for their patients. The final diagnosis in each case was made by the attending physician *before* receipt of the serologic results.

Results

Myopericarditis group. Of the 63 consecutive cases reviewed, 45 met our criteria for the diagnosis of myopericarditis. In all of these patients the diagnosis was also made by the physicians primarily responsible for patient care. Thirty-seven of the 45 diagnosed cases were thought clinically to involve the pericardium primarily; eight cases were felt to be primarily myocarditis. In one patient, a diagnosis of myopericarditis was made although no electrocardiogram (ECG) was taken. This patient was a 38-year-old woman who was in a full body spica cast. She had pleuritic precordial chest pain, a temperature of 102° F, a loud 3 component pericardial friction rub, and cardiomegaly.

All of the other patients in the myopericarditis group had ECG abnormalities. Thirty-eight patients showed ST segment elevation and/or T wave changes. Six patients showed only low voltage QRS and/or atrioventricular conduction defects, and/or intraventricular conduction defects.

Fig. 1 summarizes the 63 patients according to the final diagnosis. Of the 45 patients with myopericarditis, 20 (44 per cent) had serologic evidence of Coxsackie B infection (16 of 37 with clinical pericarditis, 4 of 8 with clinical myocarditis). A fourfold or greater rise or fall in titer between the acute and convalescent serum samples was considered significant; high stable titers, however, were not considered significant.

Table II lists the 20 patients with Coxsackie B myopericarditis and shows their serologic response to the various B group antigens.

Non-myopericarditis group. The group of 18 patients who were found to be free of myopericarditis were initially suspected to have myopericarditis, but subsequent investigation did not support this diagnosis. These patients ranged in age from 1 year to 59 years, with a median age of 41; 12 of the 18 patients were male. Two of these 18 patients (11 per cent) were associated with Coxsackie B virus infection. One of these had pneumonia and the other suffered

The role of Coxsackie Group B virus infections in sporadic myopericarditis

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Myopericarditis associated with enterovirus infections is a well recognized entity. Coxsackie B types 1-5 are the most commonly incriminated viruses; however, there is also evidence that Coxsackie A types 1, 4, 9, and 16, Echo viruses, types 3, 6, 9, and 22, and polioviruses may cause carditis.[1-4]

While Coxsackie B viruses are known to be associated with myocardial and pericardial diseases in all age groups[5-10] particularly during outbreaks of Coxsackie virus infections, the correlation between the clinical findings and the laboratory evidence for infection has not been well clarified. This is particularly true in sporadic cases, where criteria for the etiologic diagnosis are often tenuous at best.

This study was conducted in order to determine the value of various laboratory tests used to establish a diagnosis of Coxsackie B virus infection among sporadic cases of myopericarditis. In addition, we wanted to determine if there were differences in the clinical and epidemiologic presentations of myopericarditis patients with Coxsackie B infections compared to those who had no evidence of such infections.

Methods

Patient selection and clinical information. This study is concerned with a review of 63 consecutive patients suspected of having myopericarditis, whose paired acute and convalescent serum samples were received at our laboratory between Jan. 1, 1968, and July 1, 1970. All patients were from the Seattle area and were hospitalized at a university-affiliated or a local community hospital. Clinical information about these patients was based upon a retrospective study of the outpatient and hospital medical records.

Serologic methods. The acute and convalescent serum samples were usually spaced three weeks apart, the first being drawn as soon as the possibility of myopericarditis was suspected. If symptoms had been present two or more weeks before the initial study, we tried to draw the convalescent serum samples four to six weeks later, hoping to detect a significant drop in antibody titer levels.

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Table II Serologic findings in Coxsackie B myopericarditis patients

Patient no.	Age	Sex	Antibody titer to Coxsackie virus*							
			B		B		B		B	
			Acute	Convalescent	Acute	Convalescent	Acute	Convalescent	Acute	Convalescent
1	11½	M	128†	512	64	32	64	32	2,048	512
2	13½	F	64	16	32	32	256	128	16	16
3	17	F	256	64	128	64	128	64	32	16
4	21	M	4	4	512	2,048	32	128	16	32
5	23	F	4	4	128	16	16	8	16	8
6	31	M	64	16	32	32	64	64	32	32
7	32	M	4	16	64	64	16	16	32	64
8	38	F	64	32	128	32	128	64	8	4
9	50	F	256	256	128	32	128	32	64	32
10	51	M	16	4	32	8	128	128	64	32
11	51	F	128	64	128	128	512	512	1 024	256
12	53	M	64	256	4	4	64	64	4	4
13	55	M	64	128	4	4	64	256	16	16
14	55	F	1 024	1 024	256	128	128	32	8	8
15	56	F	4	4	8	32	16	32	8	8
16	57	M	256	128	32	32	256	64	4	4
17	65	M	256	256	16	128	32	32	4	4
18	66	M	32	64	32	8	128	64	16	8
19	68	M	128	128	128	32	128	64	4	4
20	76	M	16	8	16	32	16	64	8	8

*Reciprocal of dilution.
†Boldface figures indicate instances in which significant titer changes were detected.

5 of 25 (20 per cent) in the non-Coxsackie B group. This difference is significant to a level of $\chi^2 = 5.96$, $p = 0.014$.

The common characteristics of myopericarditis such as chest pain, fever, pericardial friction rub, elevated erythrocyte sedimentation rate, and cardiomegaly all had a high incidence in both groups. Of interest is the relatively frequent occurrence of pericardial effusion (45 per cent of Coxsackie B patients, 40 per cent of the serologically non-responsive group). In the majority of cases of pericardial effusion the diagnosis was confirmed by either fluoroscopy or echocardiogram.

A history of an antecedent upper respiratory illness (URI) or viral syndrome was recorded for the majority (13 of 20 or 65 per cent) of patients with Coxsackie B myopericarditis. The onset of this symptomatology ranged from 1 to 30 days before hospital admission with a mean of 12 days prior to the onset of chest pain or signs and symptoms referable to the heart. A history of an antecedent viral syndrome was also common among the non-Coxsackie B patients (10 of 25 or 40 per cent) beginning a mean of 11 days prior to cardiac symptoms. Unfortunately information pertaining to the occurrence of antecedent viral illness was not recorded for many patients in both groups. Only 6 patients specifically denied any such symptomatology. 5 of these were in the non-Coxsackie B group.

Attempts were made to isolate viruses from feces and throat swabs of 35 of the 45 myopericarditis patients and from 3 samples of pericardial fluid, all attempts were unsuccessful. All viral cultures were obtained during hospitalization and thus were taken more than two weeks after the initial onset of symptoms of a viral illness in most cases.

Multiple blood cultures obtained from 17 cases were all negative for bacterial

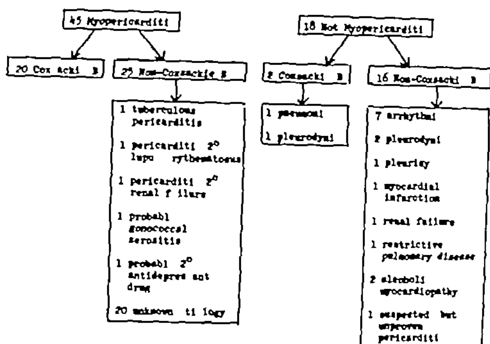


Fig. 1. Final diagnosis of 63 consecutive cases of possible myopericarditis. 2° = due to.

from acute pleurodynia. The 16 remaining non-myopericarditis patients who had no evidence of Coxsackie B infection included 7 patients with unexplained cardiac arrhythmias, 2 with pleurodynia, one with pleurisy, one with myocardial infarction, one with renal failure with a transient friction rub, one with restrictive pulmonary disease, two with probable alcoholic myocardiopathy, and one with suspected but unproved pericarditis.

The incidence of Coxsackie B infection in the myopericarditis group (20 of 45 patients or 44 per cent) was significantly greater than that in the non-myopericarditis group (2 of 18 patients or 11 per cent). This difference is statistically significant to a level of $\chi^2 = 4.90$, $p = 0.027$.

Epidemiology. The 45 myopericarditis patients were analyzed in regard to many parameters in an effort to compare and contrast the Coxsackie B associated group with those having no serologic evidence for Coxsackie B infection. Fig. 2 illustrates the distribution of the onset of symptoms according to the time of year. It is apparent that in both groups the cases were relatively distributed at random, with no seasonal preponderance.

There was a preponderance of males among the Coxsackie B myopericarditis patients (12 of 20 or 60 per cent). However, the non-Coxsackie B patients were also mostly males (18 of 25 or 72 per cent).

There was an interesting difference in the age of the patients in the two groups (Fig. 3). Eleven of the 20 Coxsackie B patients were over 50 years of age, whereas only 4 of the 25 non-Coxsackie B patients were in this age group. This difference is statistically significant to a level of $\chi^2 = 5.95$, $p = 0.014$. The majority of the non-Coxsackie B patients (14 of 25 or 56 per cent) were in the 31 to 50 age group. The median ages of the two groups were 51 and 41 years, respectively.

Signs, symptoms, and laboratory data. Tables III, IV, and V provide a comparison of the seropositive and seronegative groups of myopericarditis patients according to their symptoms, signs, and laboratory and radiologic findings. The tables show the percentage of patients in each group manifesting these various characteristics. The two groups differ significantly only with regard to the incidence of arthralgia and myalgia. Eight of the 20 Coxsackie B patients (40 per cent) experienced arthralgia, whereas only one of 25 non-Coxsackie B patients (4 per cent) experienced this symptom. (This difference is significant to a level of $\chi^2 = 6.89$, $p = 0.009$.) Likewise, 12 of 20 (60 per cent) in the Coxsackie B group reported myalgia, compared to only

Table III *Percentage of myopericarditis patients displaying various symptoms*

Myopericarditis patients	Symptom							
	Dyspnea	Orthopnea	Cough	Diaphoresis	Chest pain	Headache	Arthralgia	Myalgia
Coxsackie B group (N* = 20)	60	46	35	15	80	25	40	60
Non-Coxsackie B (N = 25)	48	16	36	29	88	16	4	20

*Number of patients in group.

Table IV *Percentage of myopericarditis patients displaying various signs*

Myopericarditis patients	Signs						
	Tachycardia	Systolic murmur	Pericardial friction rub	Fever	Gallop rhythm	Edema	Rash
Coxsackie B group (N* = 20)	80	40	70	85	15	50	10
Non-Coxsackie B (N = 25)	64	28	76	64	28	24	0

*Number of patients in group.

Table V *Percentage of myopericarditis patients with certain laboratory and radiologic findings*

Myopericarditis patients	Laboratory data		Radiologic data		
	Elevated erythrocyte sedimentation rate	Elevated white blood count >10,000	Cardiomegaly	Pericardial effusion	Pleural effusion
Coxsackie B Group (N* = 20)	85	75	75	45	65
Non-Coxsackie B Group (N = 25)	90	56	76	40	44

*Number of patients

patients died. Two patients, both of whom were being treated with corticosteroids, experienced four relapses each within one year.

Follow-up data were also available on 17 of the non-Coxsackie B patients, also for an average period of 6.6 months. Eight of these patients experienced recurrent myopericarditis; of these four were receiving corticosteroid therapy. A relapse of symptoms tended to occur when the corticosteroid dosages were reduced.

Mortality rates. Four of the myopericarditis patients in this series died, all within four months of the onset of cardiac symptoms. Three of the deaths were in the Coxsackie B associated group, but in only one of these was myopericarditis thought to be related to the patient's death. This single instance was the previously mentioned 11½-year-old boy who developed severe congestive heart failure.

The only death among the non-Coxsackie myopericarditis patients was a 36-year-old man who succumbed to a pituitary chromophobe adenoma.

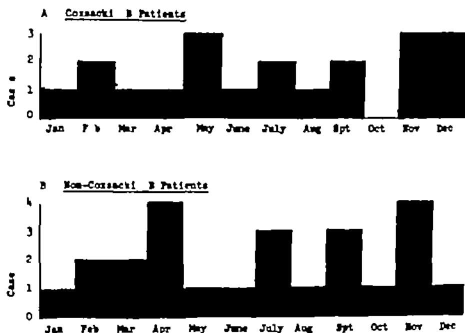


Fig. 2. Distribution of myopericarditis cases by month of onset.

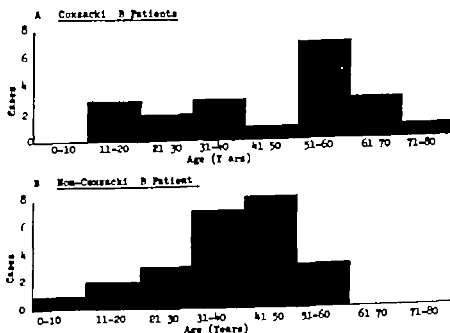


Fig. 3. Age distribution of myopericarditis patients.

growth. In 16 patients, antistreptolysin-O (ASO) titers were determined but none were significantly elevated.

In 3 patients the serum glutamic oxalacetic transaminase (SGOT) levels were elevated in the range of 216 to 330 units per milliliter. Each of these patients had severe congestive heart failure and it was postulated that the elevated SGOT level could represent abnormal liver function secondary to cardiac failure. In two of the patients, this value promptly returned to normal when the congestive heart failure was successfully treated. The third patient was an 11½ year-old boy who died. At autopsy he had extensive transmural myocardial fibrosis.

Recurrences. A number of the myopericarditis patients returned for outpatient clinic visits following their hospital discharge. Ten of the Coxsackie B patients were observed for an average of 6.6 months and three of these patients experienced a recurrence of myopericarditis, none of the

not surprising since the cardiac involvement was usually not manifest until 11 to 14 days after the onset of a viral syndrome. It has been suggested that viremia and virus excretion may have ceased by the time of the onset of myopericarditis.[23]

The finding of Coxsackie B infection in only 11 per cent of our non-myopericarditis population is consistent with the findings of other investigators. Bell and Grist[14] found that only about 10 per cent of the patients they studied with other cardiac or non-cardiac disease had evidence of enteroviral infection. This was in contrast to the rather high frequency of enteroviral association in acute pleurodynia (8 of 10) in acute myocarditis (20 of 30) and in acute pericarditis (8 of 32)

The results of our present study are comparable to several other reports of Coxsackie B virus-associated cardiac disease summarized in Table VI Helin Savola and Lapinleimu[14] described 16 cases of myopericarditis during a Coxsackie B$_5$ epidemic in Finland in 1965 Sainani and associates[11] reported 22 sporadic cases of heart disease believed to be due to Coxsackie B virus infection. Five of the cases in the latter report would not have been acceptable in our study because they were diagnosed on the basis of high titer alone or on a twofold rise from an initially high titer The authors also stated that they had 35 patients with a suspected clinical picture of viral heart disease who showed no titer rise. Hence the prevalence of Coxsackie B infection in 22 of 57 cases (39 per cent) in their study is comparable to our incidence of 44 per cent. These findings, plus the relatively high incidence of enteroviral-associated infections reported by Bell and Grist, are strikingly different from some of the earlier reports. Johnson and associates in 1961 found evidence of Coxsackie B infection in only 1 of 34 sporadic cases of acute pericarditis.

We believe that the finding of a relatively high incidence of Coxsackie B infections among myopericarditis patients affirms the value of routine serologic tests of paired serum samples for antibodies to Coxsackie B viruses in such cases. Tests for Coxsackie A and Echo viruses would also be useful, but in most areas these tests are not economically feasible on a routine basis.

Summary

In a retrospective study of 63 consecutive cases of possible cardiac disease 20 of 45 patients with myopericarditis had serologic evidence of associated Coxsackie B virus infection Only 2 of the non-myopericarditis patients had serologic evidence of Coxsackie B infection. (The difference in incidence between the two groups was statistically significant, $\chi^2 = 4.90$ $p = 0.027$) In evaluating the myopericarditis patients, arthralgia and myalgia were symptoms which occurred much more frequently with associated Coxsackie B infections Also the majority of the Coxsackie B patients were over 50 years of age, whereas most of the other myopericarditis patients were in the 31 to 50 age group

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Table VI. Data on Coxsackie B myopericarditis patients reported by other authors

Investigator	Epidemiologic data			Symptoms signs		
	No. of patients	Age range (yr)	% males	Chest pain (%)	Fever (%)	Pericardial friction rub (%)
Helin et al.[11]	18	8-65	67	67	100	78
Sainani et al.[12]	22	15-66	59	77	82	36

Non-Coxsackie B myopericarditis. Causation. A question remains as to the etiology of myopericarditis in the 25 patients who did not have a serologic response to Coxsackie B antigens 2, 3, 4, or 5. In three patients the etiology was rather well defined. One was a three-year-old American Indian girl with active pulmonary tuberculosis who subsequently developed tuberculous pericarditis. Another patient was a 17-year-old girl who developed myopericarditis secondary to systemic lupus erythematosus. The third was a 53-year-old man with chronic renal failure who had recurrent pericarditis associated with hemodialysis.[14]

There were two additional instances where an etiology was suspected. One was a 33-year-old man with gonorrheal urethritis in whom the pericarditis was thought to be due to a gonococcal serositis. The other was a 36-year-old man who was felt to have myopericarditis secondary to antidepressant drugs.

In the remaining 20 non-Coxsackie B patients the etiology is unknown. It remains conjectural how many of these instances of myopericarditis may have been associated with other viral infections or with Coxsackie B infections which we were unable to demonstrate either because of the timing of our paired sera or because we did not routinely test for all six types.

Discussion

A relatively high incidence (44 per cent) of serologically documented Coxsackie B virus infection was found among patients with myopericarditis referred to us. The patients with suspected cardiac disease who were subsequently found *not* to have myopericarditis had a significantly lower incidence of Coxsackie B infection (11 per cent). These data imply that Coxsackie B viruses are a very common cause of myopericarditis. If anything, the incidence is probably underestimated in this study.

The incidence of Coxsackie B myopericarditis would have been much higher if we were willing to accept a single high titer as suggestive evidence. Seven of the 25 myopericarditis patients who failed to show a fourfold change in titer did have titers of 1:512 or greater. In several of these cases the paired sera were spaced only 11 to 14 days apart. Had they been drawn at a more appropriate interval (3 to 4 weeks), a significant change might have occurred.

Some authors including Smith,[8] Sainani and associates,[12] and Bell and Grist[16] have felt that high titers along with the clinical picture of viral myopericarditis were sufficient evidence to suggest Coxsackie B as an etiologic agent. Other investigators, however, have shown that high titers may be present in a significant proportion of the general population who have had no evidence of a recent viral illness. Ray and co-workers[17] found Coxsackie B neutralizing antibodies in the serum of 66 per cent of a population of over 400 subjects. Over 40 per cent of the population had what were considered to be high titers (1:32 or greater). It is our feeling that, due to the ubiquitous occurrence of Coxsackie B infections and the persistence of elevated titers in many individuals, a fourfold or greater change in titer must be present to establish any temporal relationship between the infection and the illness.

We were unable to isolate Coxsackie B viruses from any of the 35 myopericarditis patients where this was attempted. This is

Effect of exercise on the atrial recovery wave

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Exercise electrocardiography has been employed for nearly forty years as a tool in the diagnosis of coronary artery disease. The stress used most frequently in this country to induce electrocardiographic evidence of ischemic heart disease is the two-step test of Master.[1] Efforts to increase the sensitivity of this and other stress tests have led to the proposal of numerous criteria for the interpretation of postexercise electrocardiograms (ECG's). Attention has been focused largely on displacement and configuration of the S-T segment. It has been recognized that junctional (J) depression of as much as 0.2 mv. (2 mm.) occurs commonly in presumably healthy people. For this reason consideration has been given both to the duration and to the slope of the negative portion of the S-T segment. For example, the ratio between the duration of the depressed S-T segment and the Q-T interval has been proposed as a means of separating physiologic from pathologic electrocardiographic responses. However, use of this criterion has not reduced the frequency of false positive observations.

One possible explanation for S-T segment depression after exercise is an increase in the magnitude and duration of the atrial recovery wave (T_a). In the resting individual the P wave and T_a are ordinarily oppositely directed with an atrial gradient close to zero. This has been shown in ECG's taken on patients with complete heart block. A direct correlation has been demonstrated between the initial portion of T_a, heart rate, and the surface area of the P wave. In another study, isoproterenol caused a slight increase in P wave amplitude but a greater augmentation of T_a.

With this knowledge we undertook to study the effect of exercise on duration and magnitude of T_a in patients with second or third degree A-V block.

Materials and methods

Nine patients, ranging in age from 10 to 71 years, were studied. Six had permanent transvenous pacing electrodes in place and 3 were unpaced. Four had degenerative heart disease as the presumed cause of their A-V block, 2 had congenital A-V block, one had A-V block associated with chronic renal failure, one had severe calcific aortic stenosis, and one had acquired A-V block of unrecognized cause. None had symptomatic coronary artery disease.

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Effect of exercise on the atrial recovery wave

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Exercise electrocardiography has been employed for nearly forty years as a tool in the diagnosis of coronary artery disease. The stress used most frequently in this country to induce electrocardiographic evidence of ischemic heart disease is the two-step test of Master.[1,2] Efforts to increase the sensitivity of this and other stress tests have led to the proposal of numerous criteria for the interpretation of postexercise electrocardiograms (ECG's). Attention has been focused largely on displacement and configuration of the S-T segment. It has been recognized that junctional (J) depression of as much as 0.2 mv. (2 mm.) occurs commonly in presumably healthy people. For this reason consideration has been given both to the duration and to the slope of the negative portion of the S-T segment. For example, the ratio between the duration of the depressed S-T segment and the Q-T interval has been proposed as a means of separating physiologic from pathologic electrocardiographic responses. However, use of this criterion has not reduced the frequency of false positive observations.

One possible explanation for S-T segment depression after exercise is an increase in the magnitude and duration of the atrial recovery wave (T_a). In the resting individual, the P wave and T_a are ordinarily oppositely directed with an atrial gradient close to zero. This has been shown in ECG's taken on patients with complete heart block.[4] A direct correlation has been demonstrated between the initial portion of T_a, heart rate, and the surface area of the P wave. In another study, isoproterenol caused a slight increase in P wave amplitude but a greater augmentation of T_a.[5]

With this knowledge we undertook to study the effect of exercise on duration and magnitude of T_a in patients with second or third degree A-V block.

Materials and methods

Nine patients, ranging in age from 10 to 71 years, were studied. Six had permanent transvenous pacing electrodes in place and 3 were unpaced. Four had degenerative heart disease as the presumed cause of their A-V block, 2 had congenital A-V block, one had A-V block associated with chronic renal failure, one had severe calcific aortic stenosis, and one had acquired A-V block of unrecognized cause. None had symptomatic coronary artery disease.

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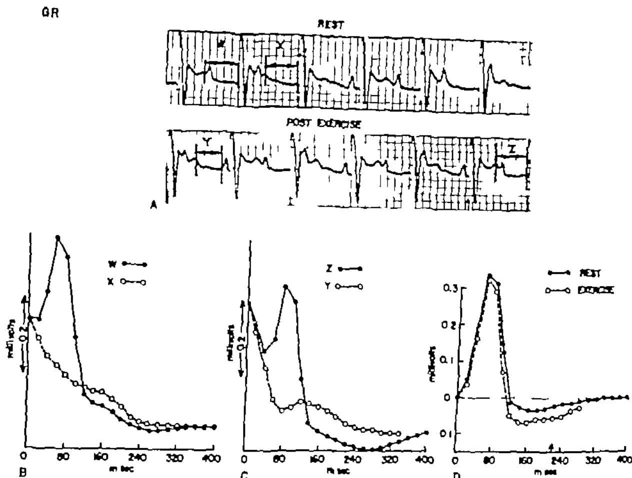


Fig. 1. A, Resting and postexercise tracings from a patient (G.R.) with an intraventricular pacemaker. Demarcated sections are replotted and superimposed as shown in B, C, and D. B, Superimposition of a segment with a P wave and T (w) on a segment without a P wave and T (x) at rest. C, Superimposition of a segment with a P wave and T (z) on a segment without a P wave and T (y) after exercise. D, The dotted line represents zero voltage (x and y from B and C). P wave and T at rest (w) and after exercise (z) are plotted as deviations from the arbitrary baseline. The arrow designates a point 220 msec. after the onset of the P wave.

Two-step exercise tests performed on 10 patients with angiographically normal coronary arteries and without heart block were used as a source of control ECG's. Measurements were made from Lead II of resting and postexercise heart rates, P wave amplitude, P-J intervals, and relative change of the J joint with exercise. These measurements were made to the nearest 0.025 mv. and the nearest 10 msec.

An exercise test, either a two-step test, walking on a treadmill, or running in place, was done on each patient with A-V block. Postexercise heart rates indicate that the intensity of exercise was comparable to the standard two-step test. ECG Lead II was recorded before and immediately after exercise. In all instances the postexercise tracings were taken within 30 seconds of the completion of exercise. To minimize measurement errors the paper was run at 50 mm. per second with a calibration of 20 mm. per millivolt.

Selected portions of the ECG were transposed to graph paper to permit superimposition of cardiac cycles in which P waves and T were absent upon cycles in which they were present. At least three pairs of temporally matched portions of cardiac cycles were plotted for each patient to evaluate the magnitude and duration of T_a. This procedure as applied to patients with pacemakers is illustrated in Fig. 1, in which the first and second cycles at rest constitute one pair. The segments without P waves were considered to represent the baseline and were arbitrarily assigned a value of zero voltage on the graphic displays. The segments replotted in Fig. 1 were chosen to illustrate the duration of T, recognizing that slight baseline distortion from the preceding T may exist in the initial portion of

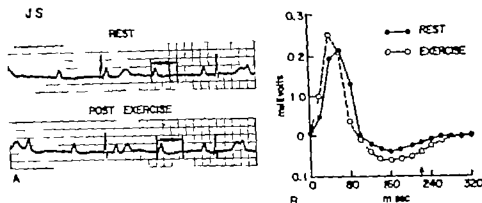


Fig. 2 *A* Resting and postexercise tracings from a patient (J S.) without an intraventricular pacemaker. Demarcated sections are replotted and superimposed in *B*. *B* Superimposition of resting and postexercise P waves and T from *A*. The arrow designates point 220 msec. after the onset of the P wave.

Segments X and Y The effect of baseline distortion by a preceding T was minimized in the analysis of each tracing by the use of other pairs of cycles, similar to cycles four and six of the resting tracing of Fig 1 in which P waves occurred at times different from those illustrated in Segments X and Y

The slow ventricular rate of the unpaced patients permitted direct measurement of P waves and T as deviations from the isoelectric baseline (Fig 2) Comparisons of resting and postexercise P waves and T were made by graphic superimposition. Three complexes were analyzed at rest and exercise for each patient and a mean value was taken for P and T_a. By this technique, measurements can be made quite accurately to 0.01 mv and 4 msec. (0.2 mm.)

The mean P J interval of the patients without A V block was used in tracings from patients with A V block to permit direct measurement not only of the maximal depth of T but also of the depth at a time corresponding to the J point.

Results

The data from the patients without A-V block are presented in Table I and those from patients with A V block, in Table II.

The resting sinus-nodal rates averaged 72 beats per minute in the patients without heart block and 85 beats per minute in those with A V block. The mean postexercise rates were 113 beats per minute in both groups. The average P J interval in the patients without heart block was 222 msec. at rest and 212 msec. after exercise. The J depression ranged from −0.1 to 0.075 mv at rest and increased by an average of 0.05 mv after exercise.

Each patient with A V block had an easily measured T at rest. The maximum depth of T ranged from 0 025 to 0 12 mv at rest, and from 0.05 to 0 19 mv at exercise. The depth of T at a time 220 msec. after the onset of the P wave ranged from 0.03 to 0.12 mv at rest and from 0.04 to 0.19 mv at exercise. The increase in T amplitude with exercise was greater than 0.05 mv in 3 of the 9 patients. T was 0.036 mv (59 per cent) greater after exercise at its point of maximal depth and 0.030 mv (55 per cent) greater at the predicted J point (220 msec. after the onset of the P wave) Two patients had a T greater than 0.15 mv after exercise. The duration of the measurable T increased in 8 of 9 patients after exercise. Particularly in the presence of short P J intervals (e.g 200 msec.) an average of 80 msec. of T will extend into the S-T segment.

Comment

The present study was undertaken to clarify the degree to which T may obscure ventricular repolarization in exercise ECG s. The data of this study indicate that as much as 160 msec. of the S-T segment may be distorted by T_a. This distortion can be at least as much as 0.19 mv at the junctional point, and progressively less thereafter

These observations on T should permit better visualization of and allowance for

Table I. Data from two step tests performed on 10 patients with angiographically normal coronary arteries

Patient	Heart rate (beats/minute)		P wave amplitude (mv)		P-J interval (msec.)		J depression (mv)	
	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
T. C.	60	92	0 125	0 125	210	210	0 0	0 025
A. C.	76	104	0 075	0 100	220	220	0 0	0 025
A. A.	76	96	0 075	0 100	210	200	0 0	0 025
E. J.	72	120	0 125	0 150	230	220	0 25	0 050
R. F.	58	106	0 050	0 125	220	200	−0 10	0 0
M. B.	70	128	0 125	0 125	240	220	0 075	0 150
K. S.	72	104	0 150	0 175	220	210	0 050	0 150
R. I.	88	130	0 100	0 150	240	230	0 0	0 050
S. K.	81	135	0 075	0 125	210	200	0 050	0 750
D. F.	66	110	0 100	0 150	220	210	0 0	0 050
Mean	72	113	0 100	0 133	222	212	0 020	0 060

Table II. Measurements of P waves and T from 9 patients with heart block

Patient	Age	State	Sinus rate	P wave amplitude (mv)	T maximum depth (mv)	T depth at 220 msec from onset of P wave (mv)	T duration (msec)
L. W.	10	Rest	75	0 19	0 120	0 100	240
		Exercise	130	0 25	0 190	0 120	270
J. S.	11	Rest	91	0 11	0 025	0 025	220
		Exercise	120	0 15	0 050	0 040	220
E. C.	25	Rest	92	0 12	0 045	0 040	230
		Exercise	110	0 12	0 065	0 060	270
E. D.	30	Rest	79	0 14	0 035	0 030	280
		Exercise	125	0 15	0 090	0 090	320
M. H.	49	Rest	75	0 07	0 045	0 040	240
		Exercise	120	0 12	0 060	0 060	280
G. R.	67	Rest	98	0 25	0 045	0 040	220
		Exercise	105	0 27	0 080	0 075	250
L. B.	67	Rest	75	0 30	0 060	0 060	300
		Exercise	86	0 34	0 080	0 070	360
A. D.	70	Rest	88	0 10	0 120	0 120	260
		Exercise	107	0 12	0 190	0 190	280
E. W.	71	Rest	95	0 15	0 050	0 040	240
		Exercise	115	0 22	0 070	0 060	300
Mean		Rest	85	0 159	0 061	0 055	248
		Exercise	113	0 193	0 097	0 085	283

T in the interpretation of postexercise ECG's.

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The left atrial lift

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Palpation of the left parasternal region is part of clinical examination of the heart. The sustained systolic thrust of right ventricular pressure overload, the high amplitude, short lived thrust of right ventricular volume overload, and the diastolic "knock" of constrictive pericarditis are well known. A systolic thrust in the left parasternal region is usually regarded as a useful sign in the assessment of the degree of right ventricular hypertrophy.

A forcible widespread late systolic lift of high amplitude has been observed in the left parasternal region in patients with severe mitral incompetence (MI) but its value in diagnosis has not been emphasized.[1-4,7] We have observed this physical sign only in patients with pure severe MI and have been impressed by its usefulness in clinical practice, particularly in the distinction between patients with MI and those with severe mitral stenosis and pulmonary hypertension overshadowed by tricuspid incompetence.

We have studied a group of 55 patients to define the characteristics of the abnormal precordial movement in the left parasternal region in normal subjects, in patients with pure MI, and in patients with pulmonary arterial hypertension due to mitral stenosis or pulmonary thromboembolism.

Material and methods

Three groups of subjects were studied. *Group 1*: normal—twelve subjects. *Group 2*: patients with right ventricular hypertrophy due to pulmonary arterial hypertension from pure mitral stenosis or pulmonary thromboembolism—19 patients. The diagnosis of mitral stenosis was confirmed by subsequent mitral valvotomy and thromboembolic pulmonary arterial hypertension by cardiac catheterization and angiocardiography. *Group 3*: pure mitral incompetence (MI) without stenosis, with or without pulmonary hypertension—24 patients.

Fig. 1 shows the distribution of the 24 patients with MI by age and race. 14 were female and 10 were male. They all had severe functional disability (Grade 3 or 4—New York Heart Association). 13 were in atrial fibrillation. 23 suffered from rheumatic heart disease; the other, an adult African, had an aneurysm of the sinus of Valsalva which rendered both aortic and mitral valves incompetent. Of the 24 patients, 5 had additional mild aortic incompetence and 7 had mild or moderate tricuspid incompetence. All the patients had the classical signs of MI with a valve orifice of at least 2 cm. in diameter.[5] The left ventricle was palpably enlarged and a pansystolic murmur, well conducted to the

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axilla and an associated third heart sound were audible. The diagnosis was confirmed by catheterization and left ventriculography in all patients. The incompetent mitral valve was subsequently replaced by a mounted aortic homograft or a Starr Edwards prosthesis.

Methods

Kinetocardiograms (KCG) were recorded on a *three-channel direct writing recorder* ('Cardiopan'—Liechti) which used a capacitance displacement transducer with a frequency response of 10 to 170 c.p.s. and a time constant of more than 1.2 sec. Recordings were made in different positions on the chest wall but in particular at the apex K45 or 55 (V_4 or V_5) and K24 (V_2). The notation is given by numerals the first indicates the electrocardiogram (ECG) "V" position and the second the intercostal space. The K24 graphs recorded movement of the left parasternal region.

ECG's, phonocardiograms (PCG) and KCG's were recorded simultaneously in held expiration. In the patients in Groups 2 and 3 recordings were made before operation and in the majority they were repeated shortly after successful valve replacement or valvulotomy.

Results

In normal subjects a brief outward deflection in K24 takes place in very early systole prior to ejection but this, and any subsequent outward thrust, is of short duration and is followed by a prolonged negative deflection associated with a small vibration at the time of pulmonary valve closure (Fig. 2).

Patients with right ventricular hypertrophy due to mitral stenosis or thrombo-embolic pulmonary arterial hypertension showed an early sustained outward deflection with a peak soon after the first sound. The rise was always early (Fig. 3 *B*) but the peak was sometimes late (Fig. 3 *A*) and often extended to the second heart sound. The excursion of the impulse was small so that much amplification was needed to show the contour and the tracings give an exaggerated and misleading view of the magnitude of the thrust. It was always very slight to the hand and was *never followed* by a sudden collapse. We

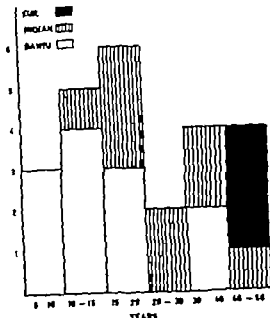


Fig. 1. Distribution of 24 patients with MI according to race and age. Note preponderance of Bantu and Indians in early and Europeans in late age groups.

did not measure the absolute amplitude of the thrust.

Every patient with severe MI showed a high amplitude outward movement in position K24. It started immediately after the first sound and continued to rise to a final peak at or just before aortic valve closure. It was followed by a precipitous collapse, the tracing falling to a nadir at a time which coincided with the third heart sound recorded phonocardiographically or with the end of the rapid filling wave on the apical KCG (Fig. 4). We have called this "The left atrial lift." It is readily appreciated at the bedside and is an easily detected sign of severe pure MI.

After mitral valve replacement the left atrial lift disappeared immediately. Recordings made soon after operation showed a minor outward thrust at K24 but this was of small amplitude and showed only the normal outward movement in presystole. It had changed in timing and had lost both its amplitude and collapsing quality. Any significant lift which remained was a consequence of tricuspid insufficiency or right ventricular hypertrophy (Figs. 5, 6, and 7). The apical left ventricular thrust at K45, 55 or 65 was unchanged in the immediate postoperative period.

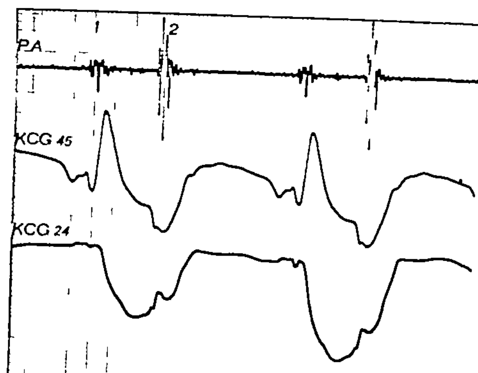


Fig 2 Lowest tracing shows a normal K24 tracing in the V position at the fourth left interspace Middle tracing from apex K45 Top tracing med um frequency PCG at pulmonary area. Paper speed 50 mm. per second.

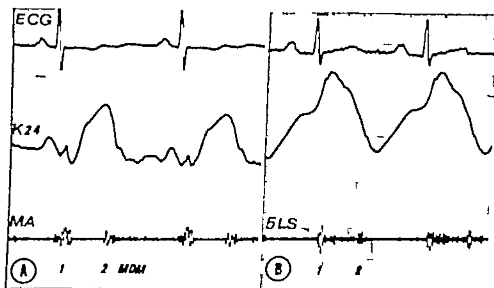


Fig 3 Tracings from position K24 in two cases of mitral tenosis confirmed at operation. A With early sharp rise but late peak just before aortic closure. B More usual contour with early peak. Moderate tricuspid incompetence reflected in PCG Both tracings are highly misleading regarding amplitude which was very low Gain has been greatly magnified to show wave form. Note atrial waves. Paper speed 50 mm. per second.

The 24 patients with MI were divided into different categories according to pulmonary arterial pressure height of left atrial V wave and radiologic left atrial size in an effort to identify factors which might influence the wave form of the left parasternal pulsation. No attempt was made to measure amplitude. The patients were first divided into 3 groups with different degrees of pulmonary hypertension (1) those with a mean pulmonary artery pressure (PAP) below 40 (11 patients) [2] those with a PAP between 40 and 60 (9 patients) and (3) those with a PAP above 60 (4 patients) No significant difference could be shown in the K24 KCG in the

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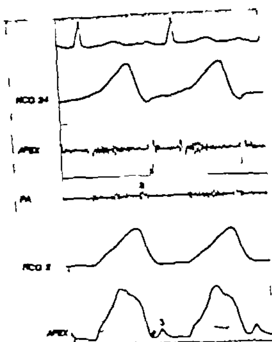


Fig. 4 Upper: Tracing at KCG24 peaks at aortic closure and collapses to third sound on mitral low frequency PCG. Lower: Apical KCG peaks 0.5 sec. before peak of parasternal KCG. Nadir of KCG24 coincides with third heart sound and not apical KCG 0 point. Paper speed 100 mm. per second.

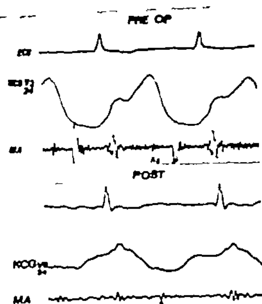


Fig. 5 Upper: Preoperative KCG24 shows double peak, the second at A being much higher. Collapse at apical third sound. Lower: Postoperative KCG24. Mitral homograft replacement. Lift now virtually impalpable and traces greatly amplified to show wave form. Early peak close to first sound. Paper speed 100 mm. per second.

three categories and the preoperative left parasternal lift gave no clue to the severity of pulmonary hypertension. The patients were again divided according to the height of the V wave in the left atrium. There was again no consistent difference and the shape of the pulsation was not related to the amplitude of the V wave. In seven patients the left atrium was aneurysmal but again the parasternal KCG showed no characteristic difference to distinguish these patients.

Discussion

We have used the kinetocardiogram because the KCG records total movement of the chest wall in relation to a fixed point in outer space. It differs from the apex cardiogram (ACG) which records movement of a small localized area in relation to its immediate surroundings, the chest wall and ribs. The transducer used for the ACG is strapped to the chest wall and cannot provide information on total displacement as it must move with the chest wall. The KCG is at great advantage when movements of any part of the chest other than the apical thrust are being analyzed. It is also more valuable than the ACG for minute analysis and comparison of events which are felt with the hand at the bedside. The hand like the KCG registers total displacement compared with the fixed point of elbow or shoulder and it is only with particular precautions that the hand can register sensations of relative movement such as the ACG.

In normal persons, brief outward deflections in K24 take place in early systole during isovolumic contraction before ejection but not during the ejection period. Normal K24 traces show a marked systolic retraction so that an outward movement during systole is paradoxic and abnormal.[4] The normal mean outward thrust at K24 is 45 msec. and any outward deflection which lasts more than 90 msec. is abnormal and due to right ventricular hypertrophy or other causes.

Pure right ventricular hypertrophy produces an early outward thrust at the left sternal edge: this is sustained, falls away

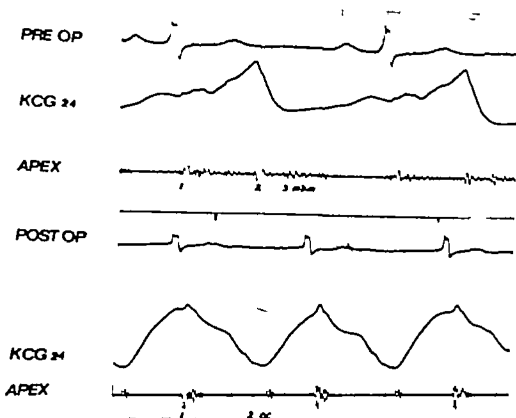


Fig 6 Upper Preoperative Parasternal peak at A_2 collapsing to apical third sound Lower Postoperative. Starr Edwards mitral valve replacement. Peak at first sound nadir at opening click. Note atrial waves. Paper speed 100 mm. per second

slowly or even mounts as systole proceeds and ends at the right ventricular 0 point [2]

In severe MI a marked but late systolic outward thrust occurs and is maximal at the time of aortic closure This left atrial lift is not sustained and collapses on to the apical third sound and not to the 0 point of the apical KCG

In MI the left atrium is forcibly over filled by the left ventricle during systole. This is well shown by comparing the apical KCG trace with K24 in Fig 4 Left ventricular action precedes the K24 lift because it causes it.

The left atrium occupies a central and *posterior position where it lies against the* unyielding spinal column As it expands during left ventricular systole it can only enlarge in a lateral and anterior direction It displaces forward the more freely mobile chambers, lifts the anterior chest wall and produces the systolic curves recorded at position K24 The early systolic part of the forward thrust may be a result of right ventricular systole. But other factors must also account for the early forward rise as some of our patients had a mean pulmonary *arterial pressure below 40 mm. Hg and did* not have significant right ventricular hypertrophy In these cases it was caused by blood flow into the left atrium in the pre-ejection and early ejection period Backward flow into the atrium increases in volume and momentum as systole proceeds. The volume of the left atrium is greatest at the end of systole and is responsible for the late peak of the left atrial lift. As soon as systole ends and the ventricular pressure falls, blood flows rapidly through the adequate mitral orifice into the left ventricle so that the left atrium anterior cardiac chambers and chest wall collapse backwards. *The trough of the backward move-*ment occurs at the end of the rapid filling wave and coincides with the apical left ventricular third sound It is not synchronous with the 0 point of the apical kinetocardiogram (Fig 4)

The bedside corollary of these kinetocardiographic findings forms the basis of a clinical sign which is useful in several different clinical situations. The left atrial lift is pathognomonic of severe MI and is seen in no other condition. It is felt in the left

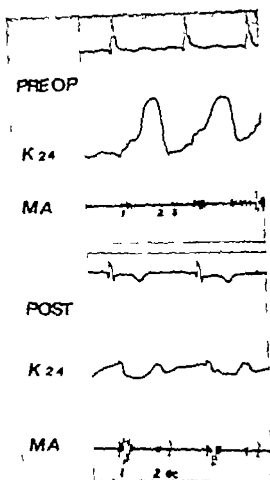


Fig. 7 Upper Preoperative. Usual late peak at A, and collapse to apical third sound. Lower Post operative. Starr Edwards mitral valve replacement. Greatly amplified to show wave form. Nearly normal tracing Paper speed 50 mm. per second.

parasternal region but is widespread and lifts the lower sternum and often the right parasternal region as well It may even extend to the right axilla, producing a general rightward and posterior movement of the whole chest wall. It is of large amplitude with a peak at or near aortic valve closure and is followed by a precipitous collapse with a nadir at the time of the apical third sound. This is quite different from the low amplitude, early and sustained thrust of right ventricular hypertrophy In many patients with mitral valve disease an apparent "right ventricular heave" has, on careful simultaneous auscultation and palpation disclosed its true identity as a left atrial lift.

Furthermore, in patients with aortic incompetence the presence of a left atrial lift has confirmed the diagnosis of significant MI sufficiently to justify mitral valve replacement.

Summary

In severe mitral incompetence a left parasternal lift is palpable. It has a high amplitude and a late peak at the time of aortic valve closure and a collapsing descent to the third heart sound. It is produced by rapid atrial expansion causing forward displacement of the heart. It disappears immediately after mitral valve replacement.

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Experimental and laboratory reports

Plasma volume changes with long term beta adrenergic blockade

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Effects of specific beta adrenergic receptor blockade have been extensively investigated and results relating to cardiac performance, vascular reactivity, and metabolic processes have been summarized in several excellent reviews.[1-4] In contrast, little is known of the effect of such blockade on plasma volume. Yet sympathetic activity and intravascular volume are closely interrelated: increased sympathetic stimulation is a prime compensatory mechanism for volume depletion, whereas volume expansion reduces autonomic reflexes.[5] On the other hand, norepinephrine infusions lead to plasma volume contraction[6,7] whereas plasma volume expansion results from interference with adrenergic function.[8] Thus, apart from chronic diuretic agents, antihypertensive therapy is usually associated with increased intravascular volume.[8-12] Since propranolol is an effective antihypertensive agent[13] in properly selected cases,[14] the question was raised in regard to its effect on plasma volume and whether the reduction of arterial pressure by nondiuretic drugs is necessarily linked with intravascular volume expansion.

An additional consideration stemmed from our previous studies showing long term reduction of cardiac output with propranolol,[14] an observation that was later confirmed for another beta blocking agent.[15,16] Although none of our treated hypertensive patients developed evidence of heart failure, cardiac decompensation has been reported to follow propranolol therapy in other types of heart disease.[1,17] Since initial results showed plasma volume contraction rather than expansion with chronic propranolol therapy, serial measurements of volume were thought to be possibly helpful in evaluating hemodynamic changes reported with that treatment. This approach was based on the classic notion that intravascular volume expansion occurs in cardiac patients only with the onset of cardiac decompensation.[8]

Methods

Propranolol was given as sole antihypertensive medication to 14 hypertensive patients in doses ranging from 20 to 160 mg four times a day for periods from 3 to 36 months. Selection of patients, details of

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follow-up and evaluation of antihypertensive effects of that drug have already been reported.[14] All patients were informed of the investigational nature of this treatment and consented to its trial most were familiar with the various procedures involved from their participation in our long term study of hypertension. Initial determinations were performed after they had discontinued their former medication for at least 4 weeks. None had any evidence of cardiac or renal decompensation as determined by appropriate examination (history and physical examination ECG chest x-ray arterial response to Valsalva maneuver serum creatinine concentration, creatinine clearance, etc.) Four had renal arterial disease the other 10 were considered to have essential hypertension. Cardiac output was determined by dye dilution (indocyanine green) before during and after therapy hemodynamic effects of long term propranolol treatment in most of these patients have already been reported.[14]

Plasma volume (RIHSA) was measured in all 14 patients immediately before treatment was begun. In 12 it was again determined sometime after 3 to 9 months of treatment and in 8 of these it was again remeasured a year later. In the other 2 patients, plasma volume was determined only after a year or more of uninterrupted therapy (Table II). Nine patients were available for repeat measurements of volume 1 to 8 weeks after discontinuance of propranolol and before another or the same therapy was begun. Determinations were always performed in the morning with the patient fasting and after 30 to 45 minutes of supine rest. Volume was computed from plasma separated from samples of blood obtained without stasis before and 10 minutes after injecting 5 μc of I[131] or 2.5 μc of I[125]. Details of the method used and reasons for expressing results in reference to body height have been already reported.[15] After determinations of volume and output isoproterenol infusion (0.03 mcg./Kg./M.) was administered intravenously to all patients both before and during therapy. Adequate beta-adrenergic blockade during therapy was thus demonstrated in all cases when there was no response to this dose which had increased the heart rate before treatment.[11]

All patients measured their arterial pressure twice daily at home and the values reported are weekly averages of those readings. Some determinations of plasma volume and occasional ones of cardiac output were performed on an outpatient basis most were obtained during short periods of hospitalization of the patients for reevaluation. In no case was any patient confined to bed or restricted in diet, and measurements were performed within the first 3 to 4 days of admission.

Statistical tests of significance were performed by paired data analysis, with each patient serving as his own control; correlation coefficients (r) were calculated by conventional methods.[22]

Results

In no instance in this group of hypertensive patients was plasma volume significantly increased by propranolol. In contrast, it was reduced by more than 8 per cent in 9 of 12 patients receiving oral propranolol for 3 to 9 months (Table I) but in only 5 of 10 who continued therapy for a year or more (Table II). This dividing line (8 per cent variation in plasma volume) is based on possible inherent errors of volume determinations.[22] Cardiac index remained lower than control values during the period of therapy (Table III). Mean arterial pressure was reduced in practically all patients[11,14] but this may only reflect a selection bias since prolonged follow-up and determinations of plasma volume were usually carried out in those who responded to treatment. Despite this limitation however it could be seen that plasma volume contraction had little relation to reduction of arterial pressure the correlation between changes in mean arterial pressure and plasma volume variation was insignificant ($r = 0.098$).

Cardiac output was practically always reduced by propranolol as previously reported. Only one patient had a marked (+29 per cent) increase in output as measured 4.5 months after beginning treatment he was also the only one in this series whose mean arterial pressure rose from 113 to 125 mm. Hg with therapy. With more prolonged treatment (more than a year) cardiac output returned to slightly above control values ...

Table I. Plasma volume (PV) and mean arterial pressure (MAP) variations with oral propranolol therapy for 3 to 9 months

Patient No.	Dose (mg./day)	Duration (mo.)	MAP (mm. Hg)		PV (ml./cm.)	
			Before therapy	During therapy	Before therapy	During therapy
1	160	6	123	104	14.3	12.9
2	160	5	140	86	14.9	13.5
3	80	8	105	76	22.1	19.7
4	240	7	116	97	15.6	13.5
5	480	4½	113	125	20.9	15.8
6	160	4	113	115	14.8	15.2
7	160	3½	140	102	16.7	13.7
8	240	4½	111	103	21.7	19.7
9	160	7	141	116	22.0	18.2
10	320	6	126	103	19.4	14.6
11	80	6	116	105	17.9	17.7
12	160	9	133	111	15.4	14.4
Average	200	5.8	123	103	17.98	15.74
S.E.M.	—	—	3.67	4.01	0.89	0.71
Paired t test				3.884		4.541
p				< 0.005		< 0.001

2 patients but remained reduced in the others. Among patients responding to treatment there seemed to be some gross correlation between plasma volume contraction and cardiac output reduction. Patients with plasma volume variations of questionable significance (±8 per cent) had scattered output variations (from +11 per cent to −39 per cent) averaging −9 per cent, whereas those with more marked plasma volume contraction (8 per cent) had greater reduction of output (average −23 per cent). However, the correlation coefficient of these two variables was not statistically significant (r = 0.134). No relation was found between changes in plasma volume and total peripheral resistance (r = −0.064). No significant variations in weight were noted among the patients during their follow-up period. The significance of this observation is, however, difficult to evaluate because of the multiple factors determining changes in weight of subjects on unrestricted diet.

Discussion

In the absence of significant changes in weight in our patients and of a recognized diuretic action of propranolol, plasma volume variations with beta adrenergic blockade were probably secondary to its peripheral vascular effects. This can only be an inferential conclusion since extracellular water volume was not determined and thus, it is not known whether the ratio of plasma to interstitial fluid volume[24] was reduced as this inference requires or remained unchanged as in the chronic hypovolemia induced by thiazide therapy.[15] There was no evidence, either clinical or radiologic, of cardiac decompensation in any of these patients. Normal response of blood pressure to the Valsalva maneuver was obtained in all before during and after propranolol therapy. Thus, heart failure with its attendant increase in sympathetic activity seems to be an unlikely possibility in these cases.

It might therefore seem reasonable to assume that beta adrenergic blockade results in plasma volume contraction secondary to unopposed alpha adrenergic activity. In addition, propranolol may further enhance vasoconstriction by blocking beta mediated peripheral vasodilation.[25] This explanation would unify under a common denominator the reduction of plasma volume by propranolol, its contraction by infusions of norepinephrine,[6,7] and its expansion by ganglionic,[9] neural[8,10,11] or

Table II. Variations in plasma volume expressed as ml./cm. with oral propranolol therapy for (A) 3-9 months and (B) one year or more

Patient No.	Before treatment (ml./cm.)	With therapy			
		A		B	
		Mo.	ml./cm.	Mo.	ml./cm.
1.	14 3	6	12 9	12	13 7
2.	14 9	5	13 5	26	13 5
3.	22 1	8	19 7	15	21 1
6.	14 8	4	15 2	14	14 5
7.	16 7	3 5	13 7	14	15 9
8.	21 7	4 5	19 7	19	19 4
10.	19 4	6	14 6	36	17 0
11.	17 9	6	17 7	31	16 2
13.	18 6	—	—	13	15 9
14.	13 8	—	—	21	14 5
Average	17 62	5 3	15 87	20	16 37
Average difference		—	−1 86	—	−1 25
S.E.D		—	0 58	—	0 34
Paired t test		—	3 14	—	3 676
P			< 0 02		< 0 01

*Patient numbers same as listed in Table I. The two additional subjects (13 and 14) received, respectively, 160 and 360 mg. daily of propranolol with reduction of mean arterial pressure from [illegible] to [illegible] mm. Hg (No. 13) and from 127 to 111 mm. Hg (No. 14).
S.E.D. Standard error of difference for paired statistical analysis. The p value refers to significance of difference from pretreatment level.

Table III. Cardiac output (CI) and total peripheral resistance (TPR) corrected for body surface area in hypertensive patients treated with oral propranolol, 80 to 480 mg./day

	Group A		Group B	
Duration of therapy	3-9 mo.		12-36 mo.	
Number of patients	11		8	
	CI (L./min./M.²)	TPR (units)	CI (L./min./M.²)	TPR (units)
Before treatment	3 15	41 3	3 22	41 5
During treatment	55	45 5	2 73	40 9
Average difference	−0 60	+4 2	−0 49	−0 6
S.E.D	0 34	3 43	0 21	—
Paired t test	3 38	1 22	2 31	—
P	<0 01	>0 2	<0 05	n.s.

S.E.D. Standard error of difference.

alpha adrenergic blockade.[23] Since propranolol is a beta-blocking agent apparently devoid of direct sympathomimetic or vascular action,[1] the magnitude of its effects would then depend on the level of uninhibited alpha adrenergic activity[24] and not surprisingly, therefore, would result in varying degrees of plasma volume alteration. The smaller degree of plasma volume contraction observed when treatment was prolonged for more than a year may be due to long term neurogenic readjustments.

That no correlation was found between plasma volume reduction and changes in

Table I. Plasma volume (PV) and mean arterial pressure (MAP) variations with oral propranolol therapy for 3 to 9 months

Patient No.	Dose (mg./day)	Duration (mo.)	MAP (mm. Hg)		PV (ml./cm.)	
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3	80	8	105	6	22.1	19.7
4	240	7	116	97	15.6	13.5
5	480	4½	113	125	20.9	15.8
6	160	4	113	115	14.8	15.2
7	160	3½	140	102	16.7	13.7
8	240	4½	111	103	21.7	19.7
9	160	7	141	116	[illegible]2.0	18.2
10	320	6	126	103	19.4	14.6
11	80	6	116	105	17.9	17.7
12	160	9	133	111	15.4	14.4
Average	200	5.8	123	103	17.98	15.74
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Paired t test				3.884		4.541
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2 patients but remained reduced in the others. Among patients responding to treatment there seemed to be some gross correlation between plasma volume contraction and cardiac output reduction. Patients with plasma volume variations of questionable significance (±8 per cent) had scattered output variations (from +11 per cent to −39 per cent) averaging −9 per cent, whereas those with more marked plasma volume contraction (8 per cent) had greater reduction of output (average −23 per cent). However, the correlation coefficient of these two variables was not statistically significant ($r = 0.134$). No relation was found between changes in plasma volume and total peripheral resistance ($r = -0.064$). No significant variations in weight were noted among the patients during their follow up period. The significance of this observation is however difficult to evaluate because of the multiple factors determining changes in weight of subjects on unrestricted diet.

Discussion

In the absence of significant changes in weight in our patients and of a recognized diuretic action of propranolol, plasma volume variations with beta-adrenergic blockade were probably secondary to its peripheral vascular effects. This can only be an inferential conclusion since extracellular water volume was not determined and thus it is not known whether the ratio of plasma to interstitial fluid volume[19] was reduced as this inference requires, or remained unchanged as in the chronic hypovolemia induced by thiazide therapy.[12] There was no evidence, either clinical or radiologic, of cardiac decompensation in any of these patients. Normal response of blood pressure to the Valsalva maneuver was obtained in all before, during, and after propranolol therapy. Thus, heart failure with its attendant increase in sympathetic activity seems to be an unlikely possibility in these cases.

It might therefore seem reasonable to assume that beta adrenergic blockade results in plasma volume contraction secondary to unopposed alpha adrenergic activity. In addition propranolol may further enhance vasoconstriction by blocking beta mediated peripheral vasodilation.[21] This explanation would unify under a common denominator the reduction of plasma volume by propranolol, its contraction by infusions of norepinephrine,[6,7] and its expansion by ganglionic,[8] neural[9,10,11] or

Table II Variations in plasma volume expressed as ml./cm. with oral propranolol therapy for (A) 3-9 months and (B) one year or more

Patient No.	Before treatment (ml./cm.)	With therapy A Mo.	ml./cm.	B Mo.	ml./cm.
1	14 3	6	12 9	12	13 7
2	11 9	5	13 5	26	13 5
3	22 1	8	19 7	15	21 1
6	14 8	4	15 2	14	13 5
7	16 7	3 5	13 7	14	15 9
8	21 7	4 5	19 7	19	19 4
10	19 4	6	14 6	36	17 0
11	17 9	6	17 7	31	16 2
13	18 6	—	—	13	15 9
14	15 8	—	—	21	16 5
Average	17 62	5 3	15 87	20	16 37
Average difference		—	−1 86	—	−1 25
S.E.D		—	0 58	—	0 34
Paired t test		—	3 14	—	3 676
p			< 0 0[illegible]		< 0 01

*Patient numbers same as listed in Table I. The two additional subjects (13 and 14) received, respectively, 160 and 360 mg. daily of propranolol with reduction of mean arterial pressure from 153 to 89 mm. Hg (No. 13) and from 127 to 112 mm. Hg (No. 14).
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	Group A		Group B	
Duration of therapy	3-9 mo.		12 36 mo.	
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Before treatment	3 15	41 3	3 22	41 5
During treatment	2 55	45 5	2 73	40 9
Average difference	−0 60	+4 2	−0 49	−0 6
S.E.D	0 34	3 43	0 21	—
paired t test	2 38	1 22	2 41	—
p	<0 01	>0 2	<0 05	n.s.

S.E.D.: Standard error of difference.

alpha adrenergic blockade.[36] Since propranolol is a beta-blocking agent apparently devoid of direct sympathomimetic or vascular action,[3,4] the magnitude of its effects would then depend on the level of uninhibited alpha-adrenergic activity[43] and not surprisingly therefore, would result in varying degrees of plasma volume alteration. The smaller degree of plasma volume contraction observed when treatment was prolonged for more than a year may be due to long term neurogenic readjustments.

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Table I Plasma volume (PV) and mean arterial pressure (MAP) variations with oral propranolol therapy for 3 to 9 months

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			Before therapy	During therapy	Before therapy	During therapy
1	160	6	123	104	14 3	12 9
2	160	5	140	86	14 9	13 5
3	80	8	105	76	22 1	19 7
4	240	7	116	97	15 6	13 5
5	480	4½	113	125	20 9	13 5
6.	160	4	113	115	14 8	15 8
7	160	3½	140	102	16 7	15 2
8	240	4½	111	103	21 7	13 7
9	160	7	141	116	22 0	19 7
10.	320	6	126	103	19 4	18 2
11	80	6	116	105	17 9	14 6
12	160	9	133	111	15 4	17 7
Average	200	5 8	123	103	17 98	14 4
S.E.M	—	—	3 67	4 01	0 89	15 74
Paired t test				3 884		0 71
p				< 0 005		4 541
						< 0 001

2 patients but remained reduced in the others. Among patients responding to treatment there seemed to be some gross correlation between plasma volume contraction and cardiac output reduction Patients with plasma volume variations of questionable significance (±8 per cent) had scattered output variations (from +11 per cent to −39 per cent) averaging −9 per cent whereas those with more marked plasma volume contraction (8 per cent) had greater reduction of output (average −23 per cent) However the correlation coefficient of these two variables was not statistically significant (r = 0 134) No relation was found between changes in plasma volume and total peripheral resistance (r = −0 064) No significant variations in weight were noted among the patients during their follow up period The significance of this observation is, however difficult to evaluate because of the multiple factors determining changes in weight of subjects on unrestricted diet

Discussion

In the absence of significant changes in weight in our patients and of a recognized diuretic action of propranolol plasma volume variations with beta adrenergic blockade were probably secondary to its peripheral vascular effects. This can only be an inferential conclusion since extracellular water volume was not determined and thus it is not known whether the ratio of plasma to interstitial fluid volume[24] was reduced as this inference requires or remained unchanged as in the chronic hypovolemia induced by thiazide therapy [22] There was no evidence either clinical or radiologic of cardiac decompensation in any of these patients. Normal response of blood pressure to the Valsalva maneuver was obtained in all before during and after propranolol therapy Thus heart failure with its attendant increase in sympathetic activity seems to be an unlikely possibility in these cases.

It might therefore seem reasonable to assume that beta-adrenergic blockade results in plasma volume contraction secondary to unopposed alpha adrenergic activity In addition propranolol may further enhance vasoconstriction by blocking beta mediated peripheral vasodilation.[24] This explanation would unify under a common denominator the reduction of plasma volume by propranolol its contraction by infusions of norepinephrine [6,7] and its expansion by ganglionic,[8] neural [9,10,11] or

tion in myocardial contractility Although plasma volume expansion during treatment with ganglion-blocking agents,[9] guanethidine,[10] alpha methyl-dopa,[11] or alpha-adrenergic blockers[8] seems to be a physiologic readjustment to lowered venomotor tone and increased venous capacity such an expansion has not been recorded during *uncomplicated propranolol* therapy Indeed an increase in intravascular volume under this condition should lead to careful reappraisal of cardiac compensation

Plasma volume contraction did not appear to be responsible for the reduction of arterial pressure in hypertensive patients. Chronic hypovolemia is one of the factors, although not the only one, responsible for the reduction of blood pressure with chronic thiazide therapy[12,44] However it did not appear to play a role in the reduction induced by long term propranolol treatment, since both hypertension and symptoms of hyperactive circulation were controlled in some patients who showed no significant variation in plasma volume.

Summary

Plasma volume was determined repeatedly before and during long-term propranolol therapy in 14 hypertensive patients, as well as after cessation and resumption of the same therapy in some of them. In no instance was plasma volume expanded by propranolol in contrast, it was reduced by more than 8 per cent in over half of the patients, so that the average for the whole group was significantly lowered during therapy extending up to 9 months ($p < 0.001$) or over a year ($p < 0.01$) No relationship was found between the contraction of plasma volume and the reduction of arterial pressure by oral propranolol The absence of plasma volume expansion with beta adrenergic blockade and even more, its actual contraction in the majority of patients contrast strikingly with its reported increase by sympathetic or alpha-adrenergic blocking agents.

We gratefully acknowledge the expert technical assistance of Miss Helen Kleinhenz, R. N and Mrs. Kathy Comella, R.N and the secretarial work of Mrs. Aldona Raulinaitis. The propranolol hydrochloride used in this investigation was kindly supplied as Inderal through H. A. Barnett, M.D and M. Baggs, of Ayerst Laboratories.

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Table IV. Plasma volume (ml/cm) variations with cessation and resumption of propranolol therapy

Patient No	Before treatment	Therapy		Therapy		
		<1 yr	>1 yr	Discontinued	Restarted	Discontinued
2	14 9	13 5	13 5	13 5	13 0	—
4	15 6	13 5	—	14 4	12 1	—
7	16 7	13 7	15 9	15 2	—	—
8	21 7	19 7	19 4	19 5	18 7	—
10	19 4	14 6	—	19	16 2	—
11	17 9	17 7	16 [illegible]	16 2	15 7	16 [illegible]
12	15 4	14 3	—	15 4	—	—
13	18 6	—	15 9	17 0	—	—

Patient numbers same as those listed in Tables I and II

total peripheral resistance is not very surprising: changes in peripheral resistance are probably not directly related to variations in plasma volume since the former is governed mainly by arteriolar tone and the latter principally reflects variations in the capacitance and exchange vessels. Studies both in man[27,28] and in animals[29,30] have demonstrated that resistance and exchange vessels do not necessarily react in the same direction.[31] Viveros and associates[32] showed that beta receptor effects on resistance vessels and precapillary sphincters could be produced by sympathetic preganglionic and postganglionic stimulation and their observations suggested that stimulation of beta receptors can influence the function of exchange vessels as well as that of resistance vessels. Both Abboud and associates[33] and Webb-Peploe and Shepherd[34] demonstrated that beta receptor stimulation does result in venodilatation. However, the magnitude of the role played by beta receptors in the venous system under normal conditions is still unsettled,[33,34] so that it might not be correct to infer from the demonstration of beta receptors in veins that increased venular resistance and capillary ultrafiltration will necessarily result from beta adrenergic blockade.

After discontinuance of therapy a persistence of volume reduction below pretreatment levels was noted in some patients (Table IV). The same was also observed in regard to cardiac output which returned to control levels in some but not in all after cessation of treatment so that average values during and after therapy were not significantly different (2 48 vs. 2 75) despite the increase of basal supine heart rate from 64 to 77 beats per minute ($p < 0 005$). However, in all patients resumption of oral propranolol therapy was associated again with further reduction in plasma volume and cardiac output (Table IV).

Whatever the mechanisms underlying variations in plasma volume, determinations of volume during propranolol treatment were practically very helpful in assessing the cardiovascular status of treated patients. The effect of propranolol on sodium balance noted by Epstein and Braunwald[35] would be expected to increase plasma volume by diminishing cardiac compensation and increasing sodium retention. This hazard, which is always possible in patients with overloaded or damaged hearts, did not occur in these hypertensive patients, possibly because none was in incipient or actual decompensation.[36] None of them developed symptoms or signs of heart failure at rest or on exertion; the Valsalva maneuver consistently gave a normal overshoot response and in no instance resulted in square wave pressure changes.[37] Contraction of the plasma volume, or failure of it to expand, was therefore an added insurance of adequate compensation[8] despite the measured reduction in cardiac output and assumed diminu

The nature and type of arrhythmias in acute experimental hyperkalemia in the intact dog

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In 1911 Mathison noted that potassium induces varying degrees of atrioventricular (A-V) block in experimental animals, by observing contraction of the atria and ventricles. Several studies have confirmed this early observation and, with the aid of the electrocardiogram,[1-4] have characterized types and degrees of conduction disorder which vary from report to report. Some studies have noted, in addition to depressed conduction, other arrhythmias that occur in the experimental animal[5] and in man. The present state of knowledge of the effects of potassium on A-V conduction[7] has recently been reviewed by Fisch. Electrophysiologic studies have revealed differences in sensitivity to potassium in specific and ordinary myocardial tissues as the cause of conduction failure within the atria and ventricles.[5-9]

The purpose of the present study was to localize areas of A-V conduction disturbance in the canine heart subsequent to intravenous infusion of potassium by using His bundle recordings obtained via electrode catheters. Multiple areas of block at different levels of A-V junctional tissues could be identified, some resulting in group beating and other irregularities of the ventricular rhythm.

Methods

Mongrel dogs weighing between 18.5 and 23.5 kilograms were anesthetized with 30 ml. per kilogram of intravenous sodium pentobarbital. The trachea was cannulated and artificial ventilation was maintained with the Harvard respirator. An end-hole catheter was inserted via the right or left femoral artery, positioned in the aortic root, and was used in obtaining samples of blood for determination of potassium. Bipolar atrial electrograms (BAE) were recorded from an electrode catheter inserted via the right jugular vein and positioned at the upper medial portion of the right atrium in such a way that large atrial (A) and small ventricular deflections were obtained. His bundle electrograms (HBE) were recorded from a tripolar electrode

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The nature and type of arrhythmias in acute experimental hyperkalemia in the intact dog

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In 1911 Mathison noted that potassium induces varying degrees of atrioventricular (A-V) block in experimental animals, by observing contraction of the atria and ventricles. Several studies have confirmed this early observation and, with the aid of the electrocardiogram,[1-4] have characterized types and degrees of conduction disorder which vary from report to report. Some studies have noted, in addition to depressed conduction, other arrhythmias that occur in the experimental animal[5] and in man. The present state of knowledge of the effects of potassium on A-V conduction has recently been reviewed by Fisch. Electrophysiologic studies have revealed differences in sensitivity to potassium in specific and ordinary myocardial tissues as the cause of conduction failure within the atria and ventricles.[8,9]

The purpose of the present study was to localize areas of A-V conduction disturbance in the canine heart subsequent to intravenous infusion of potassium by using His bundle recordings obtained via electrode catheters. Multiple areas of block at different levels of A-V junctional tissues could be identified, some resulting in group beating and other irregularities of the ventricular rhythm.

Methods

Mongrel dogs weighing between 18.5 and 23.5 kilograms were anesthetized with 30 mL. per kilogram of intravenous sodium pentobarbital. The trachea was cannulated and artificial ventilation was maintained with the Harvard respirator. An end-hole catheter was inserted via the right or left femoral artery, positioned in the aortic root, and was used in obtaining samples of blood for determination of potassium. Bipolar atrial electrograms (BAE) were recorded from an electrode catheter inserted via the right jugular vein and positioned at the upper medial portion of the right atrium, in such a way that large atrial (A) and small ventricular deflections were obtained. His bundle electrograms (HBE) were recorded from a tripolar electrode

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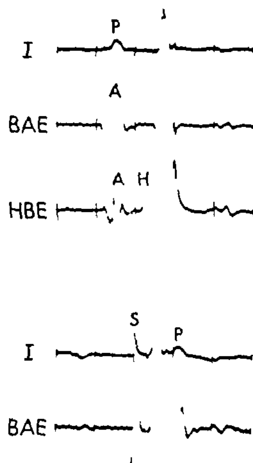


Fig. 1 Upper panel Control tracing in sinus rhythm. H-Q interval is 35 msec. *Lower panel* His bundle pacing Interval between stimulus artifact (*S*) and QRS is 35 msec. No change in QRS contour with pacing confirming catheter placement. (A sinus P wave is superimposed upon the S-T segment of paced ventricular beat.) Paper speed 150 mm./sec Time lines at 0.1 sec.

catheter with ring electrodes 2 mm wide and 1 cm apart introduced via the right femoral vein The proximal terminals of the electrode catheter were connected to a multichannel distribution switch box which allowed the selection of any two electrodes for bipolar recordings. This catheter was positioned across the tricuspid valve orifice in the manner described by Scherlag [10] Atrial (A) and His bundle potentials (H) were recorded simultaneously with a conventional ECG Lead I or Lead II on a multichannel oscilloscopic photographic recorder at paper speeds between 25 and 200 mm per second Direct electrograms were recorded at frequencies between 40 and 500 cycles per second and extremity leads at frequencies between 0 and 20 cycles per second An isotonic solution of potassium chloride was infused via the left femoral vein at rates between 0 96 and 1 6 mEq per minute (slow infusion) except for the last two experimental animals in which the infusion rate was 2 5 mEq per minute (rapid infusion) The following measurements were made (1) the interval between the first rapid oscillation in the atrial electrogram and the first rapid deflection in the His electrogram (A H) used as the measure of conduction time through the atrium and upper A V junction and (2) the interval between the beginning of H and the beginning of the QRS deflection in the His electrogram (H Q) used as a measure of conduction time below the His bundle in the specialized conduction system Twenty five experiments were performed on 6 dogs Abnormalities in rhythm (including defects in conduction) occurred 8 to 15 minutes after initiation of the slow infusion and 3 and 5 minutes after initiation of the rapid infusion Representative tracings are shown in Figs. 1 7

Results

Fig 1 demonstrates the similarity of the QRS complexes when they followed spontaneous atrial beats and during His bundle pacing as well as the similarity between the H Q interval and the stimulus to Q interval This was done in 2 of the 6 experimental animals in order to verify the placement of the recording electrodes at the His bundle. In the other 4 animals His bundle potentials were identified by the contour of the deflections and their distance from the QRS complexes during control positioning of the electrode catheters

Measurable changes in the A V conduction occurred within minutes after the start of the infusion Initially first-degree A V block was observed usually at serum potassium (K) levels between 7 9 and 10 3 mEq per liter (mEq /L.) progressing within seconds to second-degree and more advanced block with complete A V dissociation sometimes associated with accelerated ectopic impulse formation This progression was so rapid in fact that correlation of concentrations of potassium with advanced A V conduction defects and other arrhythmias was often not possible

This sequence is illustrated in the three panels of Fig 2 which are from the same

experiment. In all, the atrial rate is 200 per minute (A A is 300 msec.) In the control record (Panel *A*) the A H interval is 50 msec., and the H-Q interval is 33 msec. In Panel *B* P waves are not discernible in Lead II but atrial activity is seen in the atrial electrogram There is first-degree A V block due to prolongation of the A H interval to 160 msec. The H-Q interval is unchanged The QRS complex has become slightly widened. In Panel *C* with serum potassium of 11 mEq./L. atrial and ventricular actions are dissociated The ventricles beat regularly at the rate of 135 per minute (Q-Q equals 443 msec.) The QRS in Lead II has widened further to 80 msec. and P waves are not seen. The shape of the A deflection in the atrial electrogram varies in size with respiration but has maintained the control rate. None of the A deflections is related to an H deflection On the other hand each H deflection is followed at a constant prolonged H-Q interval of 53 msec. by a ventricular complex. Thus, one can conclude that multiple areas of block have developed in the conduction system A first-degree A V block above the recorded portion of the His bundle (Panel *B*) has progressed to complete A V dissociation in Panel *C* the atria are controlled most likely by the sinus node at its original rate of 200 beats per minute whereas the ventricles follow a slower pacemaker (rate 135 beats per minute) located in the His bundle. The H potentials are smaller and slurred and their propagation to the ventricles is impaired by a first-degree block in the His-Purkinje system

A more complex type of A V block observed in another experiment is obvious in Fig 3 The atrial rhythm is regular A H intervals alternate between 102 (A H) and 160 msec (A H) H-Q intervals are constant and normal (41 msec) Ventricular complexes alternate slightly in contour There are four possible interpretations of this record (a) the shorter (AH_1) intervals represent delayed A H conduction and the longer intervals represent a higher degree of A H block permitting His bundle escapes (*b*) the longer (AH_2) intervals represent A H conduction time, whereas shorter intervals are due to premature His bundle impulses (c) *both A-H* intervals represent A H conduction and differ

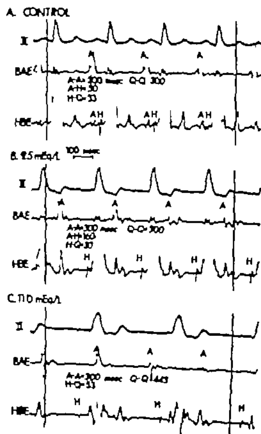


Fig. 2. Panel A Control in sinus rhythm. *Panel B* Prolonged A-H interval at serum K level of 9.5 mEq./L. *Panel C* Atrial rate same as control. H independent of A and in fixed relation to QRS. Paper speed 150 mm./sec. Time lines at 1 sec.

because of supernormal conduction in A H [11,18] (d) two A H pathways with different refractory periods and conduction speeds are used in alternate beats.[13,14]

Once complete A-V dissociation had developed additional regions of block were noted which varied in location and degree as illustrated in Figs. 4 and 5 In the extremity leads of Fig 4 P waves are barely visible. Intervals between QRS complexes shorten progressively (from 300 or 310 to 250 msec.) until a pause of 350 or 360 msec. occurs with subsequent repetition of this sequence. This suggests a conduction disturbance of Wenckebach type. The atrial electrogram shows somewhat irregular atrial activity but no A A interval is as short as the shortest interval between QRS complexes. H potentials which vary in size

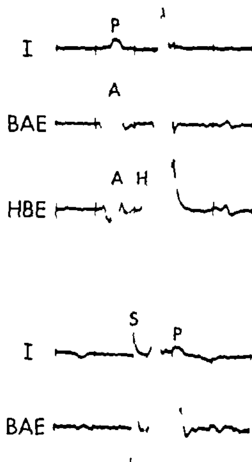


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Measurable changes in the A-V conduction occurred within minutes after the start of the infusion. Initially, first-degree A-V block was observed, usually at serum potassium (K) levels between 7.9 and 10.3 mEq. per liter (mEq./L.), progressing within seconds to second-degree and more advanced block with complete A-V dissociation sometimes associated with accelerated ectopic impulse formation. This progression was so rapid, in fact, that correlation of concentrations of potassium with advanced A-V conduction defects and other arrhythmias was often not possible.

This sequence is illustrated in the three panels of Fig. 2, which are from the same

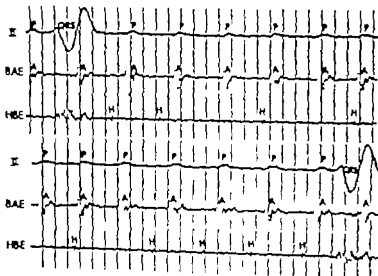


Fig. 6A. Potassium, 10.1 mEq./L., after rapid infusion. Continuous tracing, the last two P waves in upper panel being repeated in the lower. Ventricular complexes unrelated to A or H potentials. H potentials follow at prolonged interval (200-260 msec.) all but three A potentials. Second-degree A-H block, complete A V (H V) dissociation. Occasional ventricular depolarization by idioventricular impulses. Paper speed 100 mm./sec. Time lines at 0.1 sec.

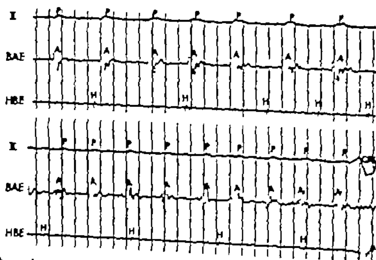


Fig. 6B In both panels, complete block below site of the recorded bundle of His. *Upper panel:* Every other then each A, potential is followed by H potential. Second-degree A-H block. A H intervals become constant with 1 : 1 conduction. *Lower panel.* Slower and regular H potentials no longer related to atrial (P and A) deflections. Complete A H dissociation with slow regular His bundle rhythm. Paper speed 100 mm./sec. Time lines at 0.1 sec.

rose rapidly (10.1 mEq./L. for Fig 6 11.8 mEq./L. for Fig 7) The two panels in Fig 6A are continuous. Throughout Fig 6, rare bizarre ventricular complexes with a widened QRS are seen in *Lead II*, independent from the faster and irregular P waves. In Fig 6A and in the upper panel of Fig 6B each or transiently every other atrial deflection is followed by an H potential at a slightly variable A H interval (200-260 msec. in Fig 6A 280 msec. in Fig 6B) In the lower panel of Fig 6B P waves have become smaller and faster while H deflections are regular slurred slower and *in no* relation to A. Thus, throughout Fig 6 there is complete

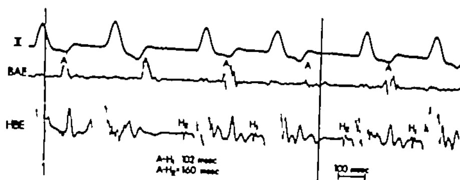


Fig 3 A H intervals (A H_1 and A H_2) alternate between 102 and 160 msec. Paper speed 200 mm./sec. Time lines at 1 sec. (Discussed in text.)

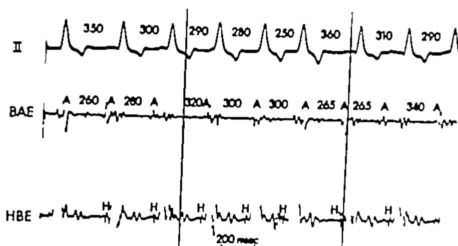


Fig 4 Groups of progressively shorter ventricular cycles alternate with a single long one. Atrial rhythm is irregular and unrelated to the ventricular rhythm. Shortest A A intervals are longer than the shortest R R intervals. All QRS complexes are preceded at constant normal interval of 36 msec. by H potentials. A H dissociation with rapid His bundle pacemaker either discharging irregularly or with exit block of Wenckebach type (*see text*) Paper speed 100 mm./sec. Time lines at 1 sec.

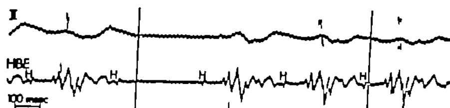


Fig 5 Second-degree block, type II below recorded area of His bundle H-Q intervals prolonged but constant. The second His potential is not followed by QRS complex. Paper speed 150 mm./sec. Time lines at 1 sec.

and shape with respiration precede each QRS complex at a constant interval without any relation to A deflections. Thus, there is complete A V dissociation the ventricles following a rapid ectopic pacemaker located in the area of the bundle of His. Either this pacemaker is irregular (the Wenckebach structure being fortuitous) or its discharges are regular with an exit block of second degree type I in a region *above* the recorded H potential Contrariwise in Fig 5 all H potentials except one are followed at constant but prolonged intervals (87 msec.) by QRS complexes. The second H potential is not propagated to the ventricles. This constitutes a second-degree block of type II *below* the area of the recorded His bundle deflection

Figs. 6*A* 6*B* and 7 are consecutive records in one experiment in which KCl was infused at the more rapid rate of 2 5 mEq /min Serum potassium concentration

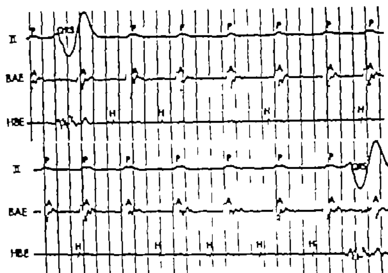


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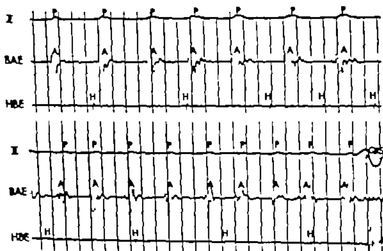


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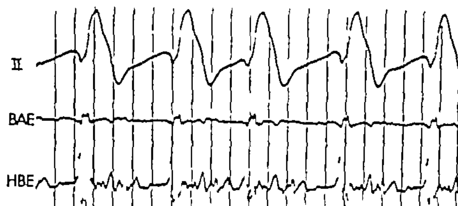


Fig 7 Same experiment as Fig 6. Potassium 11 8 mEq /L. Atrial activity and His potentials no longer recognized Idioventricular irregular rhythm. Average rate 140. See text Paper speed 100 mm./sec. Time lines at 0.1 sec

A V block distal to the His bundle with an apparent idioventricular rhythm This is combined with another blocked region proximal to or within the His bundle progressing from second-degree to complete A H dissociation

Fig 7 demonstrates irregular ventricular activity at an average rate of 140 beats per minute Here atrial activity can no longer be recognized on the atrial electrogram The His bundle electrogram is distorted by almost continuous ventricular activity Therefore the origin of this rhythm cannot be determined but the ability of the ventricles to depolarize spontaneously at a rapid rate at the same time as apparent atrial standstill is demonstrated

Discussion

Previous studies of A V conduction disturbances with hyperkalemia were done either on intact animals with analysis of ECG recordings from the body surface[2-4] or in previously thoracotomized animals with recordings obtained from chronically implanted electrodes.[15, 16] We have used the catheter technique of His bundle recordings in intact hyperkalemic animals without opening the chest

Our findings are in keeping with the previous general observations that conduction throughout the heart, including A V conduction is impaired by increase in serum potassium concentrations. The analysis of the records revealed at least two and possibly three areas between the atria and the ventricles where block may develop.

I Slow infusion of potassium (0 96 to 1 6 mEq per minute)

A H CONDUCTION The first measurable change in A V conduction was prolongation of the A H interval indicating delay above the site of His bundle recording When second-degree A V block type I progressed to a high grade A V block the area of conduction failure remained above the His bundle (Fig 2) This region appears to be the portion of the specialized conduction system most sensitive to rising levels of potassium This was noted with only slight change in the H Q intervals. At levels of potassium at which A H block greater than first degree occurred the block would not be likely to be due to an enhancement of vagal activity[17] Fisch and associates[3] who produced first-degree and second-degree A V block in the dog by the infusion of potassium intravenously demonstrated that neither interruption of the vagus nor infusion of atropine had any effect on the observed conduction defect In these studies, only standard ECGs were available but an arrhythmia with alternating long and short A V conduction times similar to our Fig 3 was recorded

Alternation of A V conduction times has been ascribed to supernormal conduction in the experimental animal[11] and in man.[12] However another explanation may be a special type of A H conduction delay as postulated by Moe and associates.[13, 14] These authors implied the presence of two functional A V pathways with different properties of refractoriness and conduction speed One of these pathways may be blocked during every other beat so that conduction is facilitated when it occurs through both pathways but is decreased in

velocity when it occurs through only one or a single pathway may be used alternately—one time with slow conduction but short refractory period and the next time with rapid conduction but long refractory period. The alternation of A H intervals seen in our Fig 3 could be explained by any of the mechanisms described above.

SINOVENTRICULAR AND INTRA ATRIAL CONDUCTION. McWilliam[13] in 1886 described in fishes a sinoventricular rhythm and similarly Vassalle and co-workers[14] interpreted certain arrhythmias during potassium intoxication as impulse propagation from the sinus node to the ventricles without atrial depolarization. In these studies, chronically implanted electrodes demonstrated sinus node activity preceding ventricular activity at a time when no P waves were seen on extremity electrocardiograms, and no atrial activity was recorded from electrodes implanted upon the muscular walls of the atria. However an electrode catheter *within the right* atrium demonstrated activity during early hyperkalemia as well as *during* advanced If the work of Sano[15] on rabbit atria is applicable to the canine atria, the explanation of atrial activity obtained selectively *from the intra* atrial electrogram may be valid A rather wide area of right atrium including the sinus node area and portions of the crista terminalis, proved to be more resistant to depression of conduction by high levels of potassium than the entire left atrium, and areas peripheral to the crista terminalis and its extensions including the right atrial epicardium The conclusion was that sinoventricular conduction may actually represent only an intra-atrial conduction defect, a view supported by Vassalle's observation[14] of intra-atrial dissociation *during* hyperkalemia.

In our experiments, the intra-atrial catheter recorded large atrial potentials at a time when P waves had disappeared from the surface ECG and continued to record these potentials at the control rat even when A V dissociation had developed (Fig) During the latter the ventricular rate was slower and QRS complexes were preceded by His bundle potentials, signifying a supraventricular pacemaker situated either in the N H region of the A V node[20] or in the bundle of His.[21] Hence, a sinoventricular rhythm postulated for advanced stages of potassium toxicity[18] was unlikely to be operative in our experiments. There appears to be evidence that a significant portion of the right atrium maintains conduction in the presence of potassium levels at which conduction to parts of the atria and even to the ventricles[17] has been interrupted

TACHYCARDIAS AND MULTIPLE AREAS OF BLOCK. A V dissociation with a supraventricular tachycardia has been observed by Fisch and associates[5] in dogs with induced hyperkalemia. During this tachycardia, they observed an ectopic rhythm with the structure of a Wenckebach phenomenon, such as in our Fig 4. If our interpretation of this arrhythmia is correct, it would be somewhat similar to those described previously in man,[22,23] in which there were two regions of block in the A V junction, the upper one being complete and the lower one of Wenckebach type. Paes de Carvalho and associates[24,25] have pointed out at least three areas in the A V junction which differ in their normal impulse propagation. This suggests that different degrees of conduction defect may occur at two or more levels in the A V junction. In the perfused rabbit heart, Watanabe[26] observed spontaneous *A V nodal rhythm.*" Impalement of several microelectrodes demonstrated that the *earliest area of depolarization* was most commonly the N H region and less commonly the A N region. It was also noted that the shape and size of propagated action potentials in a particular region of the A-V junction could change, depending upon the *location* of the pacemaker which could account for the occurrence of an exit block of a higher junctional pacemaker

The junctional pacemaker driving the ventricles in our experiments was *rapid* Pick[4] points out that excess potassium in man may produce irregular ventricular impulses with slowing *of the primary* pacemaker and acceleration of subsidiary centers. A junctional pacemaker *may* be such a subsidiary pacemaker Trautwein[27] has discussed the effects of potassium which might predispose to various types of arrhythmias. He includes the occurrence of an increase in the activity of ectopic pacemakers at a time when the predominant effect of the hyperkalemia is a decrease in the resting

membrane potential a decrease in the conduction velocity with local areas of block and a shortening of the refractory period The latter two would favor re-entry as an additional mechanism of the ectopic tachycardias produced by hyperkalemia.[21]

H-Q BLOCK. Vassalle[11] has produced various A V blocks below the bundle of His to the extent of 2 1 conduction between the bundle of His and the ventricle. In our experiments with continued rise in serum K this area of conduction failure also becomes evident. The H Q interval becomes prolonged followed by the slurring of the His potential and marked decrease in its amplitude (Fig 2 C) Eventually higher degrees of block follow—at first second degree type II (Fig 5) and then dissociation between His potentials and the slower irregular QRS complexes. The site of this block within the His Purkinje system could not be further established with our method

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Thus under the conditions of our experiments, with the possible exception of the transient acceleration of a junctional pacemaker all the arrhythmias may be explained by the defects in conduction produced by hyperkalemia The types and areas of conduction disturbances were, at least in part related to the level of hyperkalemia and to the rate of its induction.

Summary

Progressive A V block was produced in the intact dog by rapid intravenous infusion of isotonic potassium chloride (KCl) solution The site of the conduction disturbance was determined with electrode catheter recordings from the atria and region of the His bundle and a simultaneous conventional ECG First-degree and second degree A V block and then complete A V dissociation were produced with the block above the bundle of His the ventricles following a pacemaker originating in the bundle of His. During A V dissociation atrial potentials maintained their control rate. Sinoventricular conduction could not be produced under the conditions of the experiments. Further infusion of KCl produced conduction defects below the bundle of His with an irregular ventricular action Unexpectedly with the most rapid infusions of KCl the experimental animals developed complete block below the site of the His bundle recording at a time when conduction above the junctional pacemaker was only partially blocked Ventricular arrhythmias, including terminal tachycardias are probably the consequence of depressed or failing propagation of the cardiac impulse

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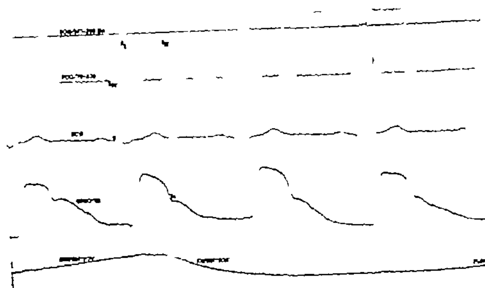


Fig 1 Representative polygram for one complete respiratory cycle. *Top to bottom*. High-frequency (140-350 Hz) and low-frequency (70-200 Hz) phonocardiograms (*PCG*) Lead II electrocardiogram (*ECG II*) carotid pulse tracing (*CAROTID*) and the respiratory trace showing one respiratory cycle (*inspiration upward*).

were recorded on a Schwarzer No 622 six-channel instrument at a paper speed of 100 mm per second Lead II electrocardiogram (ECG) apical phonocardiogram (PCG) right carotid pulse by photoelectric contact sensor and respiratory movement by a subxiphoid photoelectric contact sensor secured by an expansile belt (Figs. 1 and 2)

The initial tracing for each subject was recorded du ing normal quiet respiration. To avoid drawing attention to their breathing—thereby making an alteration of the normal rate or pattern—no mention was made nor instruction given in regard to respiration at that time. A minimum of ten complet respiratory cycles, with accompanying cardiac tracings, were recorded so that systoles could be studied during ten consecutive inspirations and expirations. Tracings were then recorded during expiratory apne to achieve which the subjects ere instructed to gently breathe in, then out and then to stop breath ng and relax this tate w s documented by the respiratory tracing which had to remain at the expir tory level

Measurements and c lculations. The mean values for five beats occurring at the peak of fi e inspirations for each subject were used to represent cardiac cycles during maximum inspiration. Similarly mean values for five beats occurring at the nadir of five different expirations for each subject were obtained to represent the cardiac cycles during maximum expiration. During expiratory apnea the means for five consecutive beats were obtained

The following measurements were made according to methods described elsewhere[7] R R nterval in milliseconds in the cycle preced ng each measured beat, to represent heart rate as 60 000/R R P R interval central pulse transmission time (PTT) pre-ejection period (PEP) left ventricular ejection time (LVET) ejection time index (ETI) the ratio of pre-ejection period to left ventricular ejection time (PEP/LVET) The respiratory cycle was established as the time between consecutive inspiration peaks on the respiratory trace. The ratio of heart rate to respiratory rate (HR/rr) was also calculated

Bl nding procedure The bl nding procedure required that the observer determine the duration of all systolic intervals being measured during a given respiratory state for each subject without knowledge of the values for those same events during the other respiratory phases. Each set of five beats was designated by an independent observer and measured by another observer blindly with respect to respiratory phases. For example the observer read the

Effects of normal breathing and expiratory apnea on duration of the phases of cardiac systole

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Boston, Mass.

The effect of respiration and various respiratory maneuvers on blood flow, pressure, and heart rate has been the basis of many investigations.[1-4] The influence of different respiratory states on the cardiac intervals, however, has not been the subject of a controlled study. The first aim of this investigation, therefore, was to determine, in a blinded study, the effects of normal inspiration and expiration on the phases of systole.

The conventional approach to studying cardiac function by noninvasive techniques calls for making recordings during expiratory apnea. This form of suspended breathing eliminates respiratory artifacts while enhancing baseline stability. Unfortunately, many individuals are unable to cooperate in suspending breathing while recordings are made or, when attempts are made to achieve apneic states, Valsalva-type strain effects are introduced. Thus it sometimes becomes necessary to make recordings during ordinary breathing. The second purpose of this investigation, therefore, was to determine, in a blinded study, the effects of conventional expiratory apnea on the cardiac systolic intervals as compared to the effects of normal inspiration and expiration. Since measurements were read to the nearest 5 msec., the blinding procedure (to be described) eliminated potential skewing of results as a manifestation of observer bias.

Methods and procedures

We studied a group of patients who were clinically stable but could be expected to have a relatively wide range of values for systolic intervals: 22 males and 8 females, ages 53 to 73, who were ambulatory outpatients with established coronary heart disease (CHD). These were otherwise unselected subjects who appeared consecutively for regular visits and were in no distress. The diagnosis of CHD had been established on the basis of stable myocardial infarction by electrocardiographic criteria, historically documented infarct including appropriate enzyme and ECG abnormalities, or episodic angina with corresponding electrocardiographic changes.

Recordings. Subjects were asked to assume a comfortable supine position on the examining table. The following tracings

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Table I. Values and differences for cardiac intervals during inspiration, expiration, and expiratory apnea

Cardiac intervals	Mean	S.D	S.E.	t	p
R-R intervals					
a. Inspiration	819 60	157 40	28 70		
b. Expiration	827 30	158 60	29 00		
c. Expiratory apnea	833 30	159 70	29 20		
a vs. b				2 56	< 0 02
a vs.				1 92	< 0 1
b vs. c				0 70	~ 0 5
Pulse transmission time					
a. Inspiration	18 82	5 55	1 01		
b. Expiration	20 43	6 16	1 12		
c. Expiratory apnea	20 13	6 19	1 13		
a vs. b				2 35	< 0 05
vs. c				1 37	< 0 5
b vs.				0 37	> 0 5
Pre-ejection period					
a. Inspiration	97 90	18 17	3 32		
b. Expiration	93 70	16 73	3 05		
c. Expiratory apnea	96 00	16 64	3 04		
vs. b				5 34	< 0.001
vs. c				1 88	< 0 1
b vs.				3 22	< 0 001
Left ventricular ejection time					
a. Inspiration	274 5	30 10	5 40		
b. Expiration	281 63	33 81	6 17		
c. Expiratory apnea	273 06	31 73	5 79		
a vs. b				4 22	< 0 001
vs. c				0 79	< 0 5
b vs.				4 46	< 0 001
Ejection time index					
a. Inspiration	366 36	18 24	3 33		
b. Expiration	372 06	20 97	3 83		
c. Expiratory apnea	362 56	20 35	3 72		
a vs. b				3 01	< 0 01
vs. c				1 89	< 0 1
b vs. c				3 03	< 0 001
PEP/LVET					
a. Inspiration	36 13	8 58	1 57		
b. Expiration	33 46	7 60	1 39		
c. Expiratory apnea	35 70	8 18	1 49		
a vs. b				4 85	< 0 001
vs. c				0 70	< 0 5
b vs. c				4 47	< 0 001

Mean R-R intervals represent heart rates of 73.93, 73.2, and 74.63 for inspiration, expiration, and expiratory apnea, respectively

relation between respiratory rate and left ventricular ejection time (LVET) during inspiration and expiration ($r < -0.2$ for both). By contrast the expected high correlation for the group between heart rate (HR) and LVET did exist for all three respiratory states, i.e., $r = -0.88$ during inspiration, $r = -0.86$ during expiration, and $r = -0.82$ during expiratory apnea.

There were highly significant differences ($p < 0.01$ or $p < 0.001$) among the three respiratory states for most of the other cardiac parameters measured. These differences are illustrated in Fig. 3 and can be summarized as follows.

Pre-ejection period (PEP). The PEP during normal expiration was shorter than the PEP during inspiration ($p < 0.001$) by a

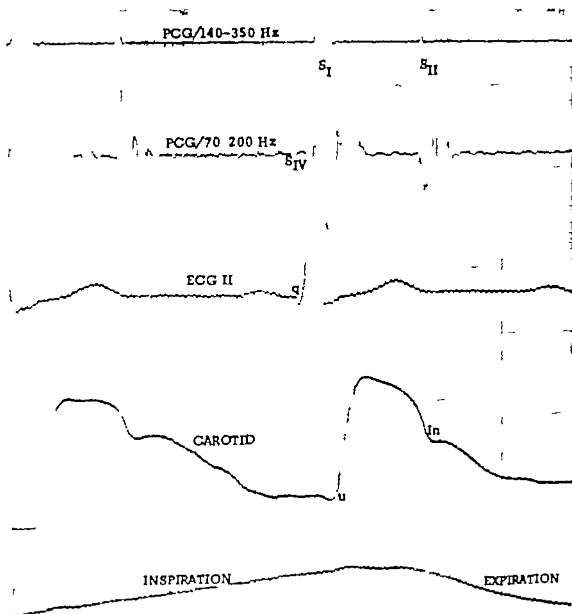


Fig. 2 Enlargement from Fig 1 showing a typical cardiac cycle (*labeled beat*) at peak of inspiration. Tracings are as described in Fig. 1 The time from the q wave on the electrocardiogram (*ECG*) to the following points were measured onset of the first rapid component of S_I and S_{II} rapid upstroke (*u*) and incisura (*In*) of carotid tracing Systolic intervals were determined from these measures (*see text*)

five beats for expiration without knowing the results for that subject during inspiration or expiratory apnea. Likewise the beats for inspiration were read without the observer's knowledge of the results during expiration or expiratory apnea and so on Student's t test was applied to the data to determine whether statistically significant differences existed between measurements made for inspiration vs. expiration expiration vs. expiratory apnea and inspiration vs. expiratory apnea for each of the cardiac systolic phases and indices.

Results

Measurements and calculations of the respiratory and cardiac events are summarized in Table I There were no significant differences at the 1 per cent level in the grouped data among inspiration expiration and expiratory apnea for the R R interval (heart rate) and for the pulse transmission time. Analysis of the data showed very poor correlation between respiratory rate and heart rate in both inspiration and expiration ($r = -0.27$ and -0.25 respectively) and equally poor cor

Table I. Values and differences for cardiac intervals during inspiration, expiration, and expiratory apnea

Cardiac intervals	*Mean*	*S.D.*	*S.E.*	*t*	*p*
R-R intervals*					
a. Inspiration	819.60	157.40	28.70		
b. Expiration	827.30	158.60	29.00		
c. Expiratory apnea	832.30	159.70	29.20		
a vs. b				2.56	< 0.01
a vs.				1.91	< 0.1
b vs. c				0.70	~ 0.5
Pulse transmission time					
a. Inspiration	18.82	5.55	1.01		
b. Expiration	20.43	6.16	1.12		
c. Expiratory apnea	20.13	6.19	1.13		
vs. b				2.35	< 0.05
vs. c				1.37	< 0.5
b vs.				0.37	> 0.5
Pre-ejection period					
a. Inspiration	97.90	18.17	3.32		
b. Expiration	93.70	16.73	3.05		
c. Expiratory apnea	96.00	16.64	3.04		
vs. b				5.34	< 0.001
vs.				1.85	< 0.1
b vs.				3.22	< 0.001
Left ventricular ejection time					
a. Inspiration	274.5	30.10	5.50		
b. Expiration	281.63	33.81	6.17		
c. Expiratory apnea	273.06	31.73	5.79		
a vs. b				4.22	< 0.001
vs. c				0.79	< 0.5
b vs. c				4.46	< 0.001
Ejection time index					
a. Inspiration	366.36	18.24	3.33		
b. Expiration	372.06	20.97	3.83		
c. Expiratory apnea	363.56	20.35	3.72		
vs. b				3.01	< 0.01
vs.				1.89	< 0.1
b vs.				5.03	< 0.001
PEP/LVET					
a. Inspiration	36.13	8.58	1.57		
b. Expiration	33.46	7.60	1.39		
c. Expiratory apnea	35.70	8.18	1.49		
vs. b				4.85	< 0.001
vs. c				0.70	< 0.5
b vs.				4.47	< 0.001

*Mean R-R intervals represent heart rates of 73.01, 72.2, and 4.63 for inspiration, expiration, and expiratory apnea, respectively.

relation between respiratory rate and left ventricular ejection time (LVET) during inspiration and expiration ($r < -0.2$ for both). By contrast, the expected high correlation for the group between heart rate (HR) and LVET did exist for all three respiratory states, i.e., $r = -0.88$ during inspiration, $r = -0.86$ during expiration, and $r = -0.82$ during expiratory apnea.

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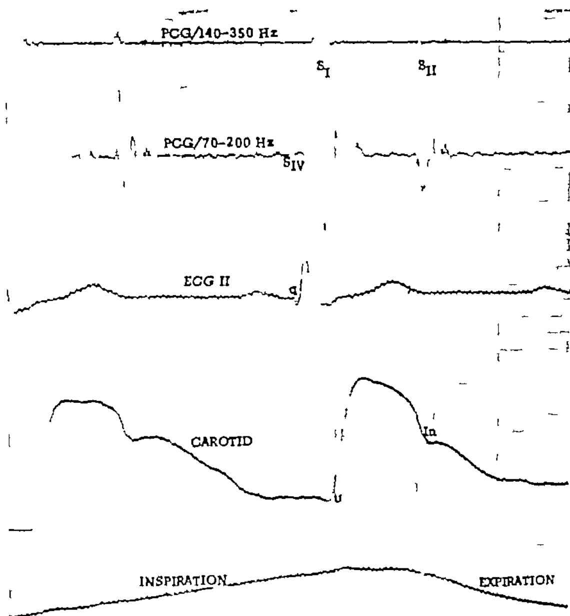


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considering measurements of systolic time intervals, particularly in patients with values near the borderline of normal

Heart rate The trivial differences in cardiac cycle length and hence heart rate are consistent with the manifest absence of respiratory sinus arrhythmia in these subjects, i e there is a negligible effect of peak respiratory swings on heart rate as well as negligible changes with short term expiratory suspension of breathing Davies and Neilson demonstrated that inspiration is associated with fluctuations in heart rate whereas expiration has little or no independent effect on heart rate. They also observed that, when a controlled respiratory rate increased beyond 8 breaths per minute the inspiratory responses merged and by 16 breaths per minute these individual inspiratory effects on rate became superimposed on each other to the point of destructive interference. The mean quiet breathing rate for our subjects was 17 9 breaths per minute Hence if distinct inspiratory effects on heart rate did occur they may have been masked by the superimposition described above accounting for the negligible rate difference between inspiration and expiration The mean heart rate for subjects during expiratory apnea did not differ significantly from the value obtained during normal quiet breathing Davies and Neilson found that heart rate did not oscillate during apnea i.e. that when the effects of the last pre apneic inspiration were completed the heart rate remained stable until the next inspiration The absence of significant differences between heart rates during quiet respiration and during expiratory apnea would be consistent with Davies and Neilson's demonstration that inspiratory effects on heart rate tend to be dispersed over the entire respiratory cycle.

By contrast with heart rate phasic respiratory effects on other parameters were clearly separable It is not surprising that these parameters need not behave like heart rate. Indeed heart rate would tend to be more rapidly responsive to respiratory change because of its marked sensitivity to nervous and humoral influences and to changes in right heart dynamics. In contrast, the immediate hemodynamic effects of respiratory changes on right heart filling would only influence left ventricular func-

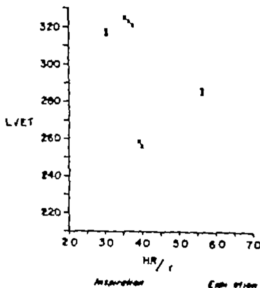


Fig 4 Comparison of the ratio of heart rate to respiration rate (*HR/rr*) to left ventricular ejection time (*LVET*) during inspiration and expiration for all subjects. No relationship could be demonstrated (see text).

tion after a lag of one,[3] two or three[1] beats. This delay in transmission to the left ventricle of changes in right heart output could reasonably be expected to be related to the ratio of heart rate to respiratory rate.

Heart rate–respiratory rate relationships Respiratory rate (rr) was compared with the heart rates for inspiration and expiration (which were virtually the same) There was a very weak relationship respectively $r = -0.268$ and -0.252. This indicates only about a 6 per cent reciprocal covariance which is negligible.

The ratio of heart rate (HR) to respiration rate (rr) was next calculated for both inspiration and expiration and plotted against the corresponding left ventricular ejection time (LVET) for all subjects (Fig 4) LVET was chosen because it showed the largest absolute differences among the respiratory states studied Nearly all HR/rr ratios fell in a relatively wide range 3 0 to 6 0 cardiac cycles per respiratory cycle (abscissa Fig 4) with a large scatter indicating no relationship between HR/rr and LVET Thus it appears that this ratio was not the factor which affected the time of appearance of changes in cardiac parameters measured between inspiration and expiration.

The expected relationship of LVET to

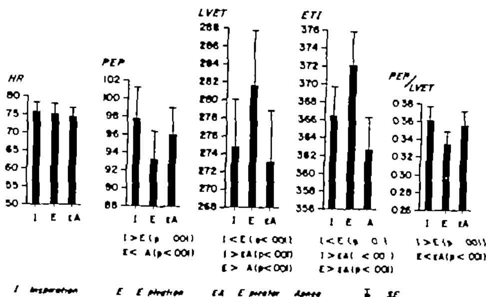


Fig. 3. Respiratory effect of normal quiet inspiration (*I*), expiration (*E*), and expiratory apnea (*EA*) on heart rate (*HR*), pre-ejection period (*PEP*), left ventricular ejection time (*LVET*), ejection time index (*ETI*), and the ratio of PEP to LVET (*PEP/LVET*). Where statistically significant differences occurred, these were indicated below the abscissa.

mean difference of 4.70 msec. Similarly, the PEP during expiration was less than the PEP during expiratory apnea ($p < 0.001$) by a mean difference of 2.80 msec. There was no statistically significant difference between PEP during expiratory apnea and PEP during normal inspiration.

Left ventricular ejection time (LVET). The LVET during expiration was significantly longer ($p < 0.001$) than the LVET during inspiration by a mean difference of 7.13 msec. The LVET during expiration was also greater than the LVET during expiratory apnea ($p < 0.001$) by a mean difference of 8.57 msec. The LVET during expiratory apnea was shorter than the LVET during inspiration; although this was statistically highly significant ($p < 0.001$), the mean difference was only 1.44 msec.

Ejection time index (ETI). When left ventricular ejection time was corrected for heart rate by calculation of the ejection time index, the differences in ETI between the three respiratory states resembled those differences occurring in the uncorrected LVET. The ETI during expiration was greater than the ETI during inspiration ($p < 0.01$) by a mean difference of 5.70. The ETI during expiration exceeded the ETI during expiratory apnea ($p < 0.001$) by a mean difference of 9.50 msec. The ETI during apnea was less than the ETI during inspiration ($p < 0.001$) by a mean difference of 3.80 msec.

Ratio of PEP to LVET. The differences in PEP/LVET which occurred between the three respiratory conditions resembled the differences in PEP alone for those states. Thus, PEP/LVET during expiration was less than that during inspiration, 0.335 vs. 0.361 ($p < 0.001$). PEP/LVET during expiration was also less than that during expiratory apnea by a mean difference of 0.022 ($p < 0.001$). The mean difference in PEP/LVET during inspiration as compared to expiratory apnea was only 0.004, which was not statistically significant.

Directional trends. The results also indicate, as seen in Fig. 3, that PEP, LVET, ETI, and PEP/LVET varied in the same direction during inspiration and expiratory apnea as compared to normal expiration. Furthermore, the absolute values for these parameters during inspiration and expiratory apnea were closer to each other than to the values during expiration.

Discussion

The results indicate distinct effects of normal respiratory fluctuations on most of the parameters measured. These effects can be explained by the well-known physiologic influence of breathing on cardiac function. Although some of these effects were quantitatively small, the differences were highly significant. The practical implication of this is that phasic respiratory activity or suspension of it should be documented in

considering measurements of systolic time intervals, particularly in patients with values near the borderline of normal.

Heart rate The trivial differences in cardiac cycle length and hence heart rate are consistent with the manifest absence of respiratory sinus arrhythmia in these subjects, i.e. there is a negligible effect of peak respiratory swings on heart rate as well as negligible changes with short term expiratory suspension of breathing Davies and Neilson demonstrated that inspiration is associated with fluctuations in heart rate whereas expiration has little or no independent effect on heart rate They also observed that when a controlled respiratory rate increased beyond 8 breaths per minute, the inspiratory responses merged and by 16 breaths per minute these individual inspiratory effects on rate became superimposed on each other to the point of destructive interference The mean quiet breathing rate for our subjects was 17 9 breaths per minute. Hence if distinct inspiratory effects on heart rate did occur they may have been masked by the superimposition described above accounting for the negligible rate difference between inspiration and expiration The mean heart rate for subjects during expiratory apnea did not differ significantly from the value obtained during normal quiet breathing Davies and Neilson found that heart rate did not oscillate during apnea,[1] i.e that when the effects of the last pre apneic inspiration were completed the heart rate remained stable until the next inspiration The absence of significant differences between heart rates during quiet respiration and during expiratory apnea would be consistent with Davies and Neilson's demonstration that inspiratory effects on heart rate tend to be dispersed over the entire respiratory cycle.

By contrast with heart rate phasic respiratory effects on other parameters were clearly separable. It is not surprising that these parameters need not behave like heart rate. Indeed heart rate would tend to be more rapidly responsive to respiratory change because of its marked sensitivity to nervous and humoral influences and to changes in right heart dynamics. In contrast, the immediate hemodynamic effects of respiratory changes on right heart filling would only influence left ventricular function after a lag of one two or three beats. This delay in transmission to the left ventricle of changes in right heart output could reasonably be expected to be related to the ratio of heart rate to respiratory rate

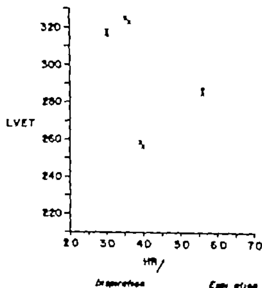


Fig 4 Comparison of the ratio of heart rate to respiration rate (*HR/rr*) to left ventricular ejection time (*LVET*) during inspiration and expiration for 11 subjects. No relationship could be demonstrated (see text).

Heart rate–respiratory rate relationships Respiratory rate (rr) was compared with the heart rates for inspiration and expiration (which were virtually the same) There was a very weak relationship respectively r = −0 268 and −0.252 This indicates only about a 6 per cent reciprocal covariance which is negligible.

The ratio of heart rate (HR) to respiration rate (rr) was next calculated for both inspiration and expiration and plotted against the corresponding left ventricular ejection time (LVET) for all subjects (Fig 4) LVET was chosen because it showed the largest absolute differences among the respiratory states studied Nearly all HR/rr ratios fell in a relatively wide range 3 0 to 6.0 cardiac cycles per respiratory cycle (abscissa Fig 4) with a large scatter indicating no relationship between HR/rr and LVET Thus it appears that this ratio was not the factor which affected the time of appearance of changes in cardiac parameters measured between inspiration and expiration

The expected relationship of LVET to

heart rate was demonstrated in this study by the significant negative correlations between LVET and HR in all three respiratory states studied. As previously mentioned, however, very poor correlations were present between respiratory rate and LVET ($r < -0.2$). This negligible relationship must also be considered as a factor contributing to the great scatter when the ratio HR/rr was compared with LVET (Fig. 4).

Pulse transmission time. Mean central pulse transmission times did not change in any of the three respiratory states. This is not surprising since the time for the pulse wave to travel from the aortic valve to the carotid artery represents a small measurement which tends to be stable under a variety of circumstances.[7, 11]

Pre-ejection and ejection periods. There is general agreement[8, 11] that the stroke volume of the right ventricle is increased with inspiration because of the decreased intrathoracic pressure which facilitates venous return to the right heart. Brecher and Hubay[3] demonstrated not only an increase in right ventricular filling during inspiration but also a concomitantly increased residual volume in the right heart. According to their study, it was not until expiration that this residual volume was ejected. Presumably then, this increased stroke volume traverses the pulmonary circuit and accounts for the increased stroke volume from the left ventricle during expiration. It has been demonstrated that the pre-ejection period (PEP) varies inversely[12] and LVET varies directly[9, 13] with stroke volume. Both the decrease in PEP and the increase in LVET during expiration as compared to inspiration are consistent with the expected increase in stroke volume at that time. Furthermore, both this expiratory decrease in PEP and increase in LVET account additively for the improvement (i.e., decrease) in the ratio of PEP to LVET from inspiration to expiration which was greater than the change in either factor.

The parallel changes of ejection time index (ETI) and LVET are explained by the lack of significant change in heart rate during any of the three respiratory states.

The best functional values for PEP, LVET, ETI, and PEP/LVET occurred during ordinary expiration, whereas both the absolute values for these parameters and the changes in them during expiratory apnea resembled those during inspiration rather than those during expiration. This resemblance seems surprising since a priori the two expiratory states might be expected to have effects in common. However, at the onset of expiratory apnea there was necessarily a brief lag in recording after the patients suspended breathing on command, after which consecutive beats were measured. Thus, the expected improvement values in left ventricular performance for phasic expiration must have been dissipated after a few apneic cardiac cycles. This could account in part for the lack of similarity of results between expiratory apnea and ordinary phasic expiration. An additional explanation for the lack of similarity arises from the comparison of the values for LVET and ETI during expiratory apnea with those during inspiration.

Values for LVET and ETI during expiratory apnea not only directionally resembled those during inspiration but were significantly lower. This may be explained both by the elimination during apnea of the normal inspiratory augmentation of right heart filling and possibly some element of straining by patients eager to cooperate. The latter would reproduce some of the conditions of the Valsalva maneuver, tending to reduce cardiac filling, which would be reflected in a decrease in stroke volume and hence in ejection time (at the same heart rate). (This behavior of ejection time coupled with the lack of significant change in PEP have in fact been demonstrated to be characteristic of Valsalva effects.[14])

Although the statistically significant differences in PEP, LVET, ETI, and PEP/LVET among the respiratory states (Table I) indicate real trends, the largest time difference among them for any cardiac parameter was less than 10 msec. This finding is in agreement with those of Hensage[15] and Cournand,[16] who indicated that in assessment of the function of the left ventricle the respiratory factor having limited influence can be ignored in practice. On the other hand, our results indicate caution in evaluating patients with borderline values, especially for PEP/LVET, which would particularly tend to fluctuate to the abnormal side in cycles recorded

during inspiration and expiratory apnea because of the reciprocal variation of the terms of this ratio (Fig 3) An example of this is the case of J F., a 54-year-old man with an old myocardial infarction whose PEP/LVET was abnormally large during expiratory apnea (0 40) and inspiration (0.41) as compared with the normal value of 0.345 ± 0.0365 S D [17] but was within normal limits (0.37) during expiration.

We had in fact selected our particular subject group because as compared to normal subjects, less homogeneity—hence, a wider range of results—could be antici pated Although the responses demon strated were explained by the physiologic effects of breathing, it is not certain that the results can be extrapolated to com pletely normal subjects. However it is precisely in the kind of patients studied that these changes are of greatest clinical importance.

Summary

The phases of left ventricular systole were measured in normal inspiration and expiration and during expiratory apnea. There were no significant differences in heart rate (*HR*) among the three respi ratory states. By contrast, pre-ejection period (PEP) left ventricular ejection time (LVET) ejection time index (ETI) and PEP/LVET showed highly significant dif ferences. Both the respiratory frequency (rr) and the ratio HR/rr had negligible independent correlations with PEP LVET ETI and PEP/LVET

The highly significant differences in PEP LVET ETI and PEP/LVET among the respiratory states indicated real trends ($p < 0.01$) or ($p < 0.001$) with values during expiratory apnea resembling those during inspiration. Functionally optimal values were obtained during phasic ex piration.

W gratefully acknowledge the technical col laboration of Eulogio H. Rectra, M.D and Abdul H. Khan, M D

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Retardation of the arterial pressure wave by propranolol

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The arterial sounds of Korotkoff are used almost universally for the indirect measurement of the arterial blood pressure. Recent studies have shown that these sounds may also offer other useful clinical information. For example, the intensities and durations of the Korotkoff sounds vary with the rate of the flow of blood into the vascular bed of the arm.[1] These signals therefore offer an indication of the general arterial blood flow and vascular conductance (flow pressure). Loud long arterial sounds indicate generalized vasodilatation as occurs in pregnancy, while weak faint sounds indicate vasoconstriction. Disappearance of the sounds serves as an early warning signal of the development of vascular collapse (shock).

When the Korotkoff sounds are recorded together with the electrocardiogram (E.C.G.), new facts concerning cardiac function are obtained. The sounds are recorded by the technique used in phonocardiography. The level of the falling mercury column is recorded on the tracing by the introduction of a standardization impulse as the cuff pressure passes each 10 mm. Hg level. A double standardization is introduced at 100 mm. Hg. The time from the onset of the QRS complex to the onset of each sound is measured. These data provide the basis for a graph of the calibrated arterial pressure upstroke contour, which is timed in the cardiac cycle (Fig. 1). In normal subjects the foot of the arterial upstroke appeared 212 ± 8 msec. after the onset of the QRS complex. Graphs obtained by this noninvasive technique differentiate valvular aortic stenosis in which the arterial upstroke may be delayed 50 msec. or more and with a slow rise in pressure from subaortic muscular stenosis in which the upstroke is early and steep.[2] The arterial pressure wave obtained by such recordings of the Korotkoff sounds is delayed in left bundle branch block and in hypothyroidism.[3,7] This method of recording also assists in the clinical assessment of congenital[8] and ischemic[9] heart disease.

Following the administration of propranolol, the timing of the Korotkoff sounds is delayed. After control arterial tracings were obtained by the method given above, 20 subjects took 40 mg. of propranolol by mouth. A tracing was taken one hour after administration of the propranolol. The interval from the onset of the QRS complex (Q) to the onset of the arterial sound at the diastolic cuff pressure (*QKD*) was delayed in all 20 normal young individuals tested

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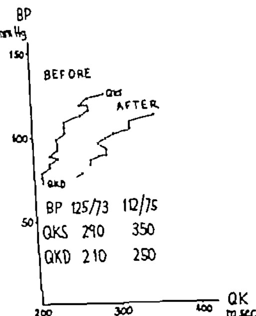


Fig. 1. Sphygmorecording before and after intake of 40 mg. of propranolol by mouth. *QKS*, interval in milliseconds from the onset of the QRS complex to the onset of the systolic Korotkoff sound. *QKD*, interval in milliseconds from the onset of the QRS complex to the onset of the diastolic Korotkoff sound. *BP*, blood pressure.

(Fig. 2) by an average of 31 ± 5 msec. The probability that these data would be obtained by chance alone is less than one per cent ($p < 0.01$).

Beta-blocking agents are known to block the positive inotropic and chronotropic effects of the catecholamines, slow the heart, reduce cardiac output, lower arterial pressure and left ventricular minute work,[11] and reduce myocardial contractility.[12,13] Ventricular peak pressure is reached more slowly after propranolol.[14]

The present finding that a single oral dose of 40 mg. propranolol delays the arterial upstroke indicates that the compound has a profound negative inotropic effect on the heart. The present discussion also calls attention to the remarkably simple methodology and great sensitivity of the technique of recording and timing the arterial pressure wave. The potential usefulness of this method for the assessment of cardiotropic drugs is indicated.

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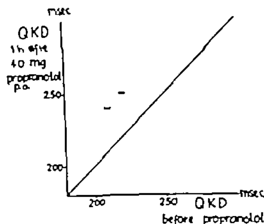


Fig. 2. Delay of the diastolic Korotkoff sound after administration of 40 mg. propranolol by mouth.

Aortic blood flow velocity during Wenckebach periods in man

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The hemodynamic consequences of atrial tachyarrhythmias have been reported previously, in particular the relationship of various intracardiac pressures to atrial rate.[1,2] Measurements of flow within various cardiac chambers and blood vessels of dogs have been made during these arrhythmias utilizing the electromagnetic flowmeter.[3,4] Initial observations in man using the Doppler ultrasonic technique have shown that when atrial tachycardia occurred, the peak flow velocity of aortic blood diminished from 20 to 60 per cent.[5]

The purpose of this report is to characterize these irregularities and specifically aortic blood flow velocity alterations during Wenckebach periods of second-degree atrioventricular block consequent to rapid atrial pacing.

Material and methods

Fifteen patients comprised the study group. Seven were normal subjects, and the other 8 had various types of cardiovascular disease. In this latter group, 3 had aortic valvular stenosis, 3 had coronary artery disease, and 1 each had aortic insufficiency and atrial septal defect.

Normal subjects were studied in the cardiac catheterization laboratory because they had chest pain of undetermined etiology or systolic murmurs thought to represent organic heart disease. All diagnoses were made on the basis of catheterization of the right and left sides of the heart, selective coronary cineangiography, and indicator-dilution curves.

Phasic aortic blood flow velocity, Lead II of the electrocardiogram, and intracardiac pressures were recorded simultaneously. All pressures were obtained with saline-filled No. 7 or No. 8 end-lumen catheters connected to a Statham P23Db strain gage. Right atrial pacing was performed with a Zucker No. 8 bipolar catheter connected to the output of an external Cordis Synchrocor II pacemaker. Fourteen patients were paced at rates of 110 to 170 per minute. A single patient with a naturally occurring Wenckebach second-degree A-V block was studied. Aortic flow velocity was obtained from the aortic root with a Doppler ultrasonic flowmeter catheter. The method and instrumentation have been described previously.[5] The procedures were performed in the cardiac catheterization laboratory with the patients under local anesthesia. The patients were in the post

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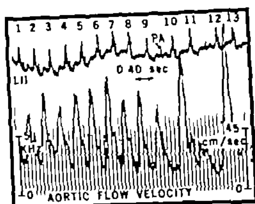


Fig 1 Lead II of the electrocardiogram (*LII*) and aortic blood flow velocity in L. S. 61 year-old man with aortic stenosis. Note the right atrial pacemaker artifacts (*PA*) occurring at rate of 150 per minute with 1 1 conduction at the beginning of the record (beats *1-4*). When the pacemaker rate was increased to 160 per minute, progressive lengthening of the P R interval took place until pacing impulse was blocked (beat *9*). Wenckebach periods at 3 2 A V conduction then occurred (beats *10-13*) Note the marked periodic increase in aortic flow velocity with the onset of this block.



Fig 2 Lead II of the electrocardiogram (*LII*) aortic pressure (*AO*) right atrial pressure (*RA*), and aortic flow velocity in E. M 59-year-old man without heart disease Note the right atrial pacemaker artifacts (*PA*) occurring at rate of 140 per minute with 3 2 atrioventricular block of the Wenckebach type. The second beat of each period results in diminished aortic pressure Increased right atrial pressure, and decreased aortic flow velocity After long R R intervals, the changes recur in cyclic fashion.

absorptive state nonsedated and in the supine position when the studies were made.

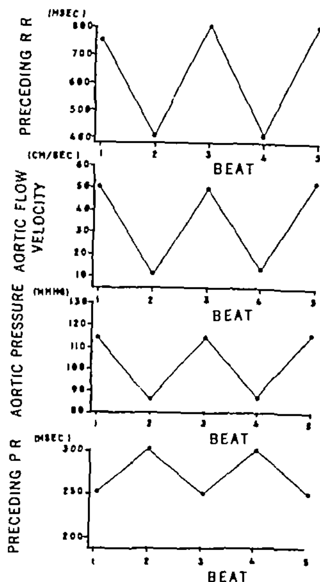
Results

Compared with the control values for rate and flow velocity right atrial pacing rates at 110 to 170 per minute with 1 1 atrioventricular conduction caused diminution of aortic flow velocity with major decrease of the systolic wave The decrease in flow velocity was directly proportional to the heart rate and this relationship continued with the onset of first-degree atrioventricular block. With the onset of type I second-degree atrioventricular block (Wenckebach periods) marked cyclic changes in aortic blood flow velocity occurred (Fig 1) The increase in peak aortic blood flow velocity was generally proportional to the preceding cycle length and inversely related to the preceding P R interval. These variations were more pronounced during shorter Wenckebach periods and most evident at 3 2 conduction (Figs. 2-4) The first beat of a period always manifested a greater peak flow velocity than did the last beat. Changes in aortic blood flow velocity paralleled those of simultaneously recorded aortic pressure tracings.

Short cycle lengths resulted in diminished aortic systolic flow velocity with reduction up to 80 per cent when compared with beats following the longest cycle length of a period There were minimal changes in aortic secondary flow velocity waves, usually no more than 12 per cent. Compared with similar pacing rates at 1 1 conduction the aortic peak flow velocity associated with the first ventricular complex following a dropped beat increased 40 per cent. Simultaneously recorded right atrial pressure was inversely related to aortic pressure and flow velocity

Comparison with naturally acquired type I second-degree atrioventricular block. A patient with rheumatic heart disease and aortic insufficiency was in sinus rhythm with the Wenckebach phenomenon. Studies of aortic blood flow velocity performed in this patient revealed cyclic periods of aortic flow velocity not unlike those previously described for artificially paced patients (Fig 5)

Influence of flow alternans In 3 patients (1 normal and 2 with aortic stenosis) aortic flow velocity alternans occurred at pacing rates of 140 to 160 per minute. One of these patients demonstrated this alternation at 1 1 conduction. With the onset



F g 3 Relationsh p of R R interv l and P R nterv l to peak aortl flow velocity and ortic pres re from records of the patient described in F g 2 The cycl c variat ons observed in the flow velocity records are confirmed by measurement

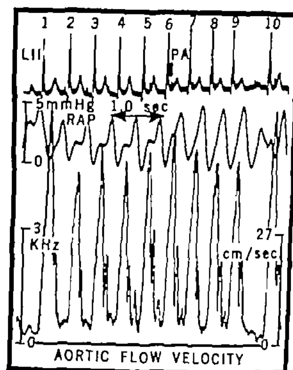
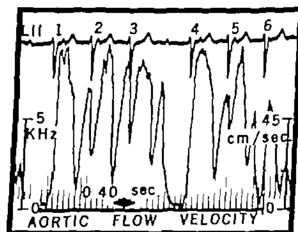


Fig 4 Lead II of the electrocardiogram (*LII*) right atrial pressure (*RAP*) and aortic blood flow elocity from D B a 20-year-old man with idiopathic heart block. Note the right atrial pacemaker artifacts (*PA*) occurring at rate of 150 per minute. There is progressive lengthening of the P R interval and bortening of the R R terval ntil a upra entricular impulse blocked after beat umber *9* The aortic blood flow velocity pattern i irregular during this long Wenckebach period. After the blocked s praventricular impulse there is a longer diastolic pause with ncrease in aortic blood flow velocity (beat umber *10*)

of Wenckebach periods the flow velocity alternation pattern changed abruptly The first ventricular systole after a blocked beat resulted in increased aortic flow veloc ity as previously described The second beat and all even numbered beats of the period demonstrated diminished aortic flow velocity compatible with low flow beats during pulsus alternans. Successive odd numbered beats in the period resulted in elevated but cyclically diminished flow velocity dependent on preceding cycle length Thus, with flow velocity alternans, cyclic variations in peak flow velocity were limited to odd numbered beats during the Wenckebach period (Fig 6)



F g 5 Lead II of the electrocardiogram (*LII*) and ortic blood flow velocity n F W 55-year-old man with aortic insufficiency Sinus hythm is present with 4 3 Wenckebach block. Not that the last beat of each cycle results i peak ortic flow elocity which is lower than that of the first beat Minimal diastolic flow wa e changes are present. These alter ations re sim lar to those obtained during trial paci g

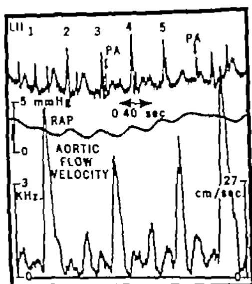


Fig. 6. Lead II of the electrocardiogram (*LII*), mean right atrial pressure (*RAP*), and aortic flow velocity in W. G., 55-year-old man without cardiovascular disease. Note the right atrial pacing artifact (*PA*) at 160 per minute with 6:5 trioventricular block. Flow velocity alternans is present. All even-numbered beats result in low aortic flow of similar magnitude. All odd-numbered beats result in higher peak flow with the last beat of the period causing lower peak flow velocity than the first beat. After beat number 5 there is a longer pause followed by increased aortic flow velocity.

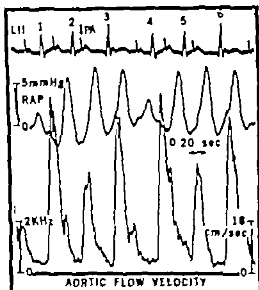


Fig. 7. Lead II of the electrocardiogram (*LII*), right atrial pressure (*RAP*), and aortic flow velocity in R. H., 13-year-old boy without heart disease. Note the pacemaker artifact (*PA*) at rate of 160 per minute with 3:2 type I atrioventricular block. After each blocked supraventricular impulse, A-V junctional beats occur at fixed coupling intervals (beat 3 and 6). Note that the junctional beats, without preceding conducted P waves, result in increased peak aortic flow velocity in a periodic fashion.

Influence of A-V junctional beats. In a single normal subject paced at 160 per minute, A-V junctional beats appeared at fixed coupling intervals of 460 msec after the blocked supraventricular beats of each Wenckebach period. These junctional beats were followed by intervals of 580 msec occurring prior to the appearance of the QRS complex of the next period. Records of aortic blood flow velocity revealed patterns which were characterized by cyclic flow related to R-R intervals similar to those previously described (Fig. 7). The junctional beats, which were not preceded by conducted P waves, resulted in peak aortic flow levels which were as high as, and in some instances more elevated than those from records of 1:1 atrioventricular conduction at similar preceding R-R intervals.

Discussion

Previous studies have stressed the adverse consequences of a rapid atrial pacing on hemodynamic indices of cardiac function. The effects of atrial tachycardia with type I second-degree atrioventricular block on aortic flow velocity must be considered in light of these studies.

Stroke volume decreases proportionally as heart rate is increased by rapid atrial pacing. The cardiac output, stroke volume, ejection time, and stroke power fall when patients are paced from the right atrium at rates greater than 110 to 120 per minute.[8] A decrease in diastolic filling time with associated diminished coronary blood flow and hypoxia probably accounts for the fall in cardiac output at these rapid rates.[9] Similarly, during atrial tachycardia there is a diminution in phasic aortic peak flow velocity when atrial pacing rates are increased above 120 per minute.[3] This is reflected peripherally by a marked decrease in arterial flow velocity to levels under 50 per cent of the control values, and at times no measurable flow can be detected in a number of beats.[6] The critical deter

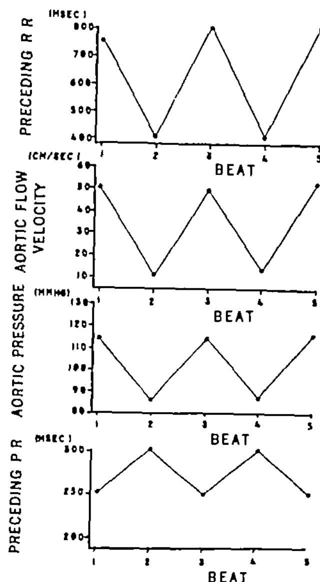


Fig 3 Relationship of R R interval and P R interval to peak aortic flow velocity and aortic pressure from record of the patient described in Fig 2 The cyclic variation observed in the flow velocity record are confirmed by measurement.

of Wenckebach periods, the flow velocity alternation pattern changed abruptly The first ventricular systole after a blocked beat resulted in increased aortic flow velocity as previously described The second beat and all even numbered beats of the period demonstrated diminished aortic flow velocity compatible with low flow beats during pulsus alternans Successive odd numbered beats in the period resulted in elevated but cyclically diminished flow velocity dependent on preceding cycle length Thus with flow velocity alternans cyclic variations in peak flow velocity were limited to odd numbered beats during the Wenckebach period (Fig 6)

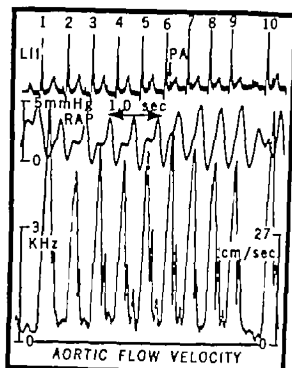


Fig 4 Lead II of the electrocardiogram (*LII*) right atrial pressure (*RAP*) and aortic blood flow velocity from D B. a 20-year-old man with idiopathic heart block Note the right atrial pacemaker artifacts (*P 1*) occurring at a rate of 150 per minute. There is progressive lengthening of the P R interval and shortening of the R R interval until supraventricular impulse is blocked after beat number *9* The aortic blood flow velocity pattern is irregular during this long Wenckebach period After the blocked supraventricular impulse there is longer diastolic pause with increase in aortic blood flow velocity (beat number *10*)

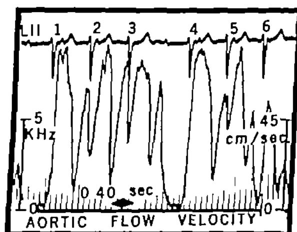


Fig 5 Lead II of the electrocardiogram (*LII*) and aortic blood flow velocity in F W 55-year-old man with aortic insufficiency Sinus rhythm is present with 4 3 Wenckebach block. Note that the last beat of each cycle results in peak aortic flow velocity *which is lower than that of the first beat Minimal* diastolic flow wave changes are present. These alterations are similar to those obtained during atrial pacing

right atrial pressure and Lead II of the electrocardiogram were measured in 7 normal subjects and 8 patients with heart disease during right atrial pacing. At pacing rates between 110 and 170 per minute type I second-degree atrioventricular block appeared. The increase in peak aortic blood flow velocity was generally proportional to the preceding cycle length and inversely related to the P-R interval. These variations were more pronounced during shorter Wenckebach periods. The first beat of a period always manifested a greater peak flow velocity than did the last beat. Short cycle lengths with less ventricular diastolic filling resulted in diminished aortic systolic flow velocity with reduction up to 80 per cent. The changes in flow velocity paralleled the changes in aortic pressure.

Compared with similar pacing rates at 1:1 conduction, the aortic peak flow associated with the first ventricular complex following a dropped beat increased 40 per cent. The conclusion is that Wenckebach periods cause cyclic changes in aortic blood flow velocity related to diastolic filling and to the length of the P-R interval.

We wish to acknowledge the technical assistance of Nancy Copeland, Larry Kartiger, Sharleen Locas, Deanna Moeller, and Sydney Peebles.

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minant for these variations in aortic flow velocity appears to be diastolic cycle length At rapid rates the shorter diastolic interval allows less time for ventricular filling end diastolic and end-systolic volumes fall and stroke volume is reduced The importance of diastolic cycle length on peripheral peak blood flow has also been confirmed during atrial premature beats, ventricular premature beats, and atrial fibrillation with a rapid ventricular response[6]

During atrial pacing whenever type I second-degree atrioventricular block ensued there were alterations in peak flow velocity related to previous diastolic cycle length This resulted in a large peak flow velocity followed by successive decreases as the diastolic intervals became shorter This latter phenomenon is clinically appreciated by cyclic increments and decrements of pulse amplitude with pauses felt by palpation

Significance of atrial contribution to aortic flow The inverse relationship of P R interval and aortic blood flow velocity during Wenckebach periods may indicate that a properly timed atrial systole is a determinant of aortic peak flow It has been suggested that maximum ventricular filling occurs when atrial contraction is completed 8 to 20 msec. before the onset of ventricular contraction[1] The significance of this increased filling has not been adequately clarified[10] In patients with complete heart block an effective atrial contraction can increase the stroke volume and aortic flow velocity by a small although appreciable amount.[6] Study of the single subject who manifested Wenckebach periods with coupled junctional beats illustrates the difficulty of comparing atrial contribution to other determinants of flow velocity The augmentation of flow velocity after a dropped beat in this patient appeared to be entirely dependent on the R R interval and especially the peak flow velocity of the preceding beat. The last beat of a given Wenckebach period was preceded by a short R R interval so that diastolic filling was incomplete, resulting in smaller left ventricular blood volumes and diminished aortic peak flow velocity These final beats of a period are hemodynamically similar to very early atrial premature systoles which cause minimal flow velocity because of short preceding cycle lengths. Minimal blood flow velocity in turn results in greater postextrasystolic augmentation of aortic peak flow velocity much the same as the junctional beat augmentation in this patient.

Flow alternans and the Wenckebach phenomenon Pulsus alternans has been observed during atrial tachycardia induced by catheter manipulation in man[11] Furthermore arterial and aortic flow measurements during pacemaker induced tachycardia have demonstrated peak flow velocity alternation during rapid rates.[5,6] Evidence has also been acquired which directly demonstrates that stroke volume varies from beat to beat during this abnormality possibly on the basis of end-diastolic fiber length alternation[12]

During Wenckebach periods, even numbered beats caused low peak flow velocities of similar magnitude regardless of preceding cycle length whereas odd numbered beats resulted in increased yet cyclic flow velocity variation Even numbered beats with low peak flow velocity had similar stroke volumes probably dependent on the same end diastolic fiber lengths dictated by the nature of myocardial contractility during alternation Odd numbered beats generally exhibited flow velocity patterns consistent with those described without the presence of flow velocity alternans. During these latter beats, end-diastolic fiber length possibly decreased in a cyclic fashion influenced by preceding cycle length Thus the combination of flow velocity alternans and type I second-degree block results in two cyclic flow velocity variables during each period Further investigation will be necessary for elucidation of this complex hemodynamic state

In conclusion Wenckebach periods are associated with cyclic variations in aortic peak flow velocity These beat to-beat alterations are related to the length of preceding diastolic intervals with long R R intervals resulting in increased peak flow velocity and short cycles causing diminished flow velocity

Summary

By means of the Doppler ultrasonic flow meter catheter phasic aortic blood flow velocity and simultaneous aortic pressure,

right atrial pressure and Lead II of the electrocardiogram were measured in 4 normal subjects and 8 patients with heart disease during right atrial pacing. At pacing rates between 110 and 170 per minute type I second-degree atrioventricular block appeared. The increase in peak aortic blood flow velocity was generally proportional to the preceding cycle length and inversely related to the P-R interval. These variations were more pronounced during shorter Wenckebach periods. The first beat of a period always manifested a greater peak flow velocity than did the last beat. Short cycle lengths with less ventricular diastolic filling resulted in diminished aortic systolic flow velocity with reduction up to 80 per cent. The changes in flow velocity paralleled the changes in aortic pressure.

Compared with similar pacing rates at 1:1 conduction the aortic peak flow associated with the first ventricular complex following a dropped beat increased 40 per cent. The conclusion is that Wenckebach periods cause cyclic changes in aortic blood flow velocity related to diastolic filling and to the length of the P-R interval.

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Case reports

Cardiac embolus

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The sudden onset of pansystolic heart murmurs is usually associated with acute bacterial endocarditis or rupture of a papillary muscle, the chordae tendineae, a semilunar cusp, or the interventricular septum. This report describes a patient who suddenly developed a pansystolic murmur associated with a precordial systolic thrill due to an embolus which lodged between the chordae tendineae of the tricuspid valve.

Emboli from systemic veins rarely lodge in the chambers of the right side of the heart. However, a few cases of systemic *emboli obstructing right ventricular out*flow have been reported.[1,2] Blumer,[3] Belt,[4] Hollister and Cull,[5] and Hudnut and associates[6] *have reported emboli caught in the* chordae tendineae of the tricuspid valve.

Case report

A 37-year-old Caucasian woman was admitted unconscious to the University of Kansas Medical Center on April 22 after referral from another hospital. She had been in her accustomed state of health until two weeks prior to admission when her usual cheerful mood changed to one of depression and she *felt exhausted. She received a short* vacation from her employer on April 16 and spent the next six days at home. The fatigue continued and she spent most of the time in bed. On April 22, she became lethargic and her husband took her to *a local hospital where she became totally unre*sponsive. The patient was then transferred to the University of Kansas Medical Center.

Physical examination at the time of admission revealed an unconscious obese woman, weighing 274 pounds, and in acute distress. The blood pressure was 110/70 mm. Hg, pulse 130 per minute, *and the respiratory rate 40 per minute. The lungs* were clear to auscultation and percussion. The point of maximum impulse (PMI) was not palpable. A soft third sound was heard by auscultation. Neurological examination revealed marked left facial weakness and flaccid hemiplegia on the left. Babinski and Hoffman signs were absent. No other pertinent physical findings were observed.

Approximately two hours after admission, the patient abruptly developed a loud pansystolic murmur and a thrill along the right sternal border. *Respiration became very labored and the patient* perspired profusely. Blood gases at this time were: Po_2, 78 per cent; Pco_2, 17 per cent; and pH, 7.54. Twenty thousand units of heparin were given intravenously and 15,000 U. subcutaneously. The central venous pressure one hour later was 22 cm. H_2O. Tachypnea continued and the patient became progressively cyanotic despite increased oxygen administration by means of assisted ventilation. Her condition continued to deteriorate and she became responsive to deep pain only. Six hours after *admission, respiration ceased and resuscitation was* unsuccessful.

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Fig. 1. In situ photograph of cardiac embolus in the right ventricle.

Autopsy findings

An autopsy performed six hours after death revealed the cause of death to be a massive pulmonary embolism occluding the main branches as well as lobar and lobular branches of the pulmonary artery. Examination of the legs revealed blood flowed freely in the right and left common iliac veins. The source of emboli was found to be a recent thrombosis of the pelvic veins, the largest of which measured 1.4 cm in diameter. An embolus, measuring 8.0 cm in length and varying in diameter from 0.8 to 1.3 cm, was found in the right ventricle. One end of the embolus was lodged between the chordae tendineae of the medial cusp of the tricuspid valve. The embolus was not attached to the trabeculae carneae of the right ventricle. Figs. 1 and 2 are photographs of the embolus. No gross abnormalities of the brain or other organs were observed.

Microscopic findings

Microscopic examination of the pelvic ... consistent with thrombi of one to three days of age. No organization of the thrombi was observed.

Sections of the brain revealed ependymitis of the hippocampus and medulla. Chronic vasculitis was observed surrounding vessels in several areas of the brain. A Holzer stain showed advanced subependymal gliosis of the hippocampus and moderate gliosis of the inferior olive and subpial cortex. There was a focal area of recent infarction in the right internal capsule. A vessel adjacent to this area was the site of a recent thrombus.

Discussion

The microscopic features of the brain, i.e., ependymitis, gliosis, and chronic vasculitis are consistent with the residua of a viral encephalitis. These changes can account for the change in mood and lethargy observed in the patient during the two-week period prior to her death. Origin of the thrombus in the cerebral vessel and

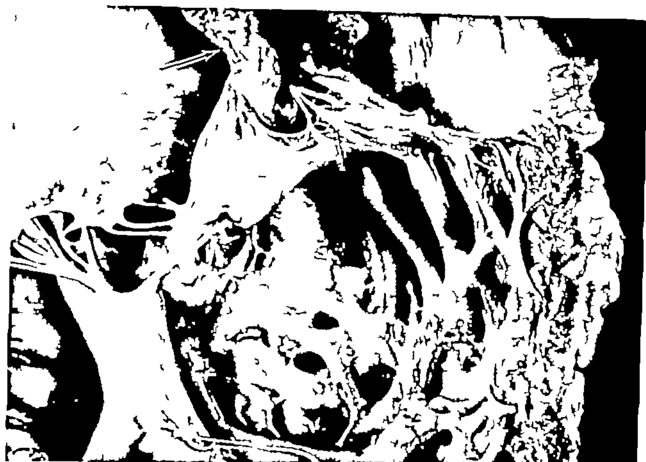


Fig 2 Close up of cardiac embolus. The distal end of the embolus has been reflected into the right atrium to demonstrate projection of the embolus between chordae tendineae of the tricuspid valve.

weakness and left hemiplegia observed at the time of admission

Pelvic vein thrombosis was the primary site responsible for cardiopulmonary embolization. The presence of a thromboembolus entwined between the chordae tendineae of the medial cusp of the tricuspid valve was an interesting accidental aspect of the embolization. Ordinarily emboli from the veins pass quickly through the right side of the heart to the pulmonary artery. Apparently this embolus passed through a gap in the chordae tendineae where it became trapped preventing adequate tricuspid valve closure. This resulted in the sudden development of a pansystolic tricuspid murmur associated with a thrill signaling cardiac embolization

Previous case reports have mentioned emboli trapped in the chordae tendineae but a review of the literature has failed to reveal any clinical findings signaling cardiac embolization. In a patient with the unexpected development of a systolic murmur the differential diagnosis should include cardiac embolus.

Summary

A case of cardiac embolization associated with the rapid development of a systolic murmur is presented. The embolus had become trapped in the chordae tendineae. This resulted in tricuspid insufficiency manifested clinically by the unforeseen appearance of a systolic murmur and thrill

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Tetralogy of Fallot with suprasystemic pressure in the right ventricle

A case report and review of the literature

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In tetralogy of Fallot the right ventricu lar systolic pressure is usually similar to that in the aorta.[1-4] The occurrence of suprasystemic pressure in the right ven tricle in this lesion has been described. The purpose of this communication is to describe a case of tetralogy of Fallot in which the peak systolic pressure in the right ventricle was considerably higher than that in the left ventricle. The septal leaflet of the tricuspid valve was unusually attached in a manner not previously de scribed and caused a partial occlusion of the ventricular septal defect.

Case report

S. R. B. (JHH 133 86 35) was 2½-year-old Puerto Rican girl known to be cyanotic since birth. A heart murmur was heard t one month. At one year increasing cyanos nd decreased activity were noted. At tw years nous angiogram done elsewhere demonstrated tetralogy of Fallot. A subsequent right subclavian-pulmonary artery end-to-side anastomosis was performed but the child was unimproved. One brief hypoxic spell was observed t 2½ years of age.

On physical examination the patient was deeply cyanotic nd had clubbing of finger and toe nails. She was in the twenty-fifth percentile (86 cm.) for height nd tenth percentile (11.2 kilograms) for weight. The temperature was 37 C., the respiratory rat was 30 per minute, the pulse rate was 100 per minute, nd the blood pressure was 102/60 mm. Hg in the arm and 120/70 in the legs. Prominent jugular a waves ere present in the semirecumbent position. A prominent right ventricular heave nd systolic thrill were palpable along the mid left sternal edge. The first heart sound was normal nd the second sound was single and loud. A prominent early systolic click followed by grade 4/6 ejection systolic murmur was heard at the left midsternal area. The lungs ere clear and the liver was not palpable.

An electrocardiogram (Fig. 1) showed right axis deviation, marked right ventricular hypertrophy and right atrial enlargement. The chest roentgenogram (Fig. 2) was compatible with the diagnosis of tetralogy of Fallot with a left aortic arch. The hematocrit was 75 per cent.

A cardiac catheterization was performed on June 30, 1969 the data from which are summarized in Table I. From the right arm vein the catheter could be easily advanced into the right ventricle nd through a entricular septal defect into the left ventricle and ascending aorta. Despite repeated attempts the pulmonary artery was not entered. The right ventricular pressure was higher than that in the left ventricle and ascending aorta and the tracing showed a triangular contour (Fig. 3). The right atrial tracing (Fig. 4) showed prominent a

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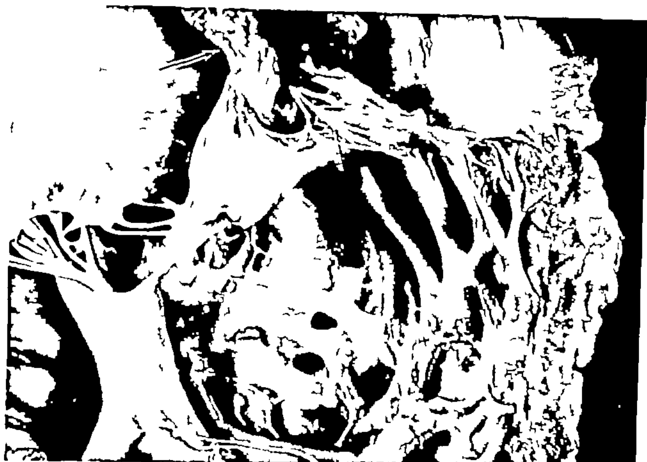


Fig. 2 Close-up of cardiac embolus The distal end of the embolus has been reflected to the right atrium to demonstrate projection of the embolus between chordae tendineae of the tricuspid valve

weakness and left hemiplegia observed at the time of admission

Pelvic vein thrombosis was the primary site responsible for cardiopulmonary embolization The presence of a thromboembolus entwined between the chordae tendineae of the medial cusp of the tricuspid valve was an interesting accidental aspect of the embolization Ordinarily emboli from the veins pass quickly through the right side of the heart to the pulmonary artery Apparently this embolus passed through a gap in the chordae tendineae where it became trapped preventing adequate tricuspid valve closure This resulted in the sudden development of a pansystolic tricuspid murmur associated with a thrill signaling cardiac embolization

Previous case reports have mentioned emboli trapped in the chordae tendineae but a review of the literature has failed to reveal any clinical findings signaling cardiac embolization In a patient with the unexpected development of a systolic murmur the differential diagnosis should include cardiac embolus.

Summary

A case of cardiac embolization associated with the rapid development of a systolic murmur is presented The embolus had become trapped in the chordae tendineae. This resulted in tricuspid insufficiency manifested clinically by the unforeseen appearance of a systolic murmur and thrill

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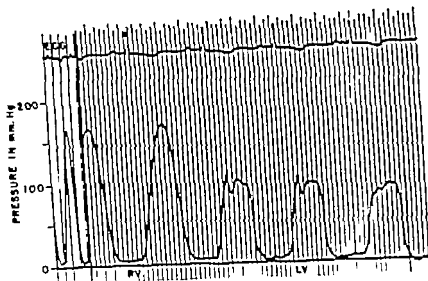


Fig. 3. The ventricular pressure tracings recorded while the catheter entered the left ventricle from the right ventricle through septal defect. Note the suprasystemic pressure in the right ventricular pressure pulse.

then made over the outflow tract. There was moderate hypertrophy of the walls of the infundibular chamber and moderately severe proximal infundibular stenosis. This was typical of tetralogy of Fallot. This tissue was widely excised to eliminate all subvalvular obstruction. The ventricular septal defect was typical one for tetralogy and approximately 1.5 cm. in diameter. The septal leaflet of the tricuspid valve did not attach to the membranous septum of the heart in the usual fashion, but extended across the ventricular septal defect and was attached to the annulus of the aortic valve.

A Teflon felt patch was used for the repair of the defect. It was necessary to cut one of the chorda of the septal leaflet of the tricuspid valve where it attached to the aortic annulus to facilitate exposure and repair of the septal defect. This chorda was then resutured to the patch and crista supraventricularis to approximate its original attachment.

The No. 16 Hegar dilator could be passed out the right ventricular outflow tract, and it was felt that this should be satisfactory for pulmonary flow. Following discontinuance of the heart-lung machine the patient immediately maintained an excellent peripheral arterial pressure and a regular sinus rhythm. When her hemodynamic status was stable, pressure measured in the aorta was 110/80, in the right ventricle 95/10 and in the main pulmonary artery 70/20. No adequate explanation was apparent for the pulmonary hypertension.

Postoperative course. The initial postoperative course was satisfactory with good urinary output and satisfactory hemodynamics. She was maintained on positive pressure ventilation via an endotracheal tube. Over the ensuing 18 to 24 hours a gradual rise in the central venous pressure occurred, with falling urinary output and clinical evidence of poor cardiac output. She responded transiently to isoproterenol infusions, but over the next 24 hours developed acidosis and evidences of poor peripheral perfusion. This course eventuated in several episodes

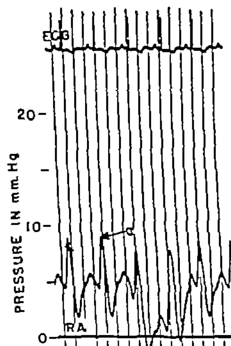


Fig. 4. Pressure tracing from right atrium shows prominent waves.

of cardiac arrest and finally at 36 hours after the operation, she could not be resuscitated from one of these episodes.

Pathology. The thoracic findings at autopsy revealed some friable clots over the thymus and arch of the aorta but did not appear to compress the outflow tract of the right ventricle. The cut section of the lungs showed four peripherally located, fresh

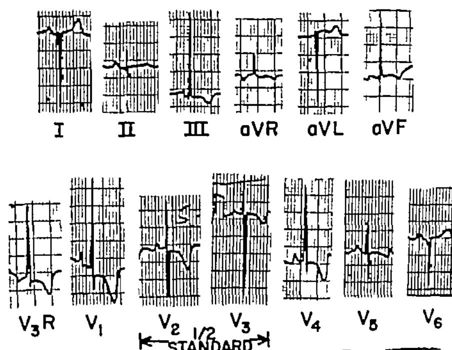


Fig *1* ECG shows right axi deviation right atrial enlargement and marked right ventricular hypertrophy

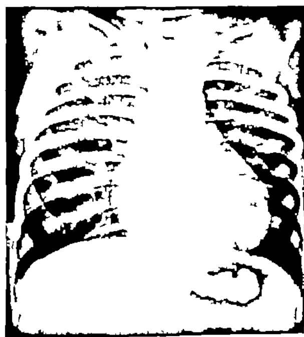


Fig *2* X-ray chest PA view bows moderate car diomegaly flat main pulmonary artery segme t left aortic arch and diminished vascularity in the l ng fields.

Table I Catheterization data

Site	*Pressure**	*O₂ satura t on (%)*
Aorta	100/65	71
Left ve tricle	100/0 to 8	53
Right ve tricle	168/0 to 8	55
Right atri m	a = 9 v = 6 m = (5)	51
Main pu lmonary artery	Not entered	

*Pressure data were obtained upon pullback of he ca heter from he ascending aorta.

waves. The angiogram from right ventricle (Fig 5) demonstrated a stenotic, domed pulmonic val e hypertrophied infundibulum, highly trabeculated right ventricle and dilated ascending aorta The aorta was posterior and to the right of the outflow tract of the right ventricle A diagnosis of tetralogy of Fallot with obstruction chiefly at the pulmonic valve level was made The suprasystemic pressure in the right ventricle was an unusual find ng and was thought probably secondary to either a small ventricular septal defect or some bnormal ty of the tricuspid valve.

On J ly 7 1969 thoracotomy was performed. The pulmonary annulus was about 11 t 12 mm n diameter and the mai pulmonary rtery was reasonably large Bypass was nstit ted with the use of a bubble oxygenator with a primi ng volume of 50 per cent Ringer lactate and 50 per cent fresh heparinized blood Perfusion wa carried out through the ascend ng aorta at a flow of 120 c.c per kilogram per mi te at normal temperature There was a remarkable degree of collateral pul monary flow which, in the absence of a ductus arteriosus on the angiogram, was felt to be bronchial It was controlled by cross-clamping the pulmonary artery above the arteriotomy The valve was bicuspid, thickened very small dome shaped, and badly deformed. Upon ope ing to the nulus, it ppeared to be compatible with reasonable flow and, accordingly a vertical ventriculotomy was



Fig. 4. Right side of heart as seen at autopsy with thickened anterior portion of septal leaflet partially adherent to thin layer of thrombus overlying Teflon repair of ventricular septal defect.

catheterization findings in the present case. At operation the septal leaflet of the tricuspid valve was observed to be attached unusually high and aberrantly on the annulus of the aortic valve rather than the septum. It is postulated that this leaflet came against the ventricular septal defect, closing it during systole thereby causing suprasystemic pressures in the right ventricle.

From the surgical standpoint it was a difficult decision to carry out a repair of the tetralogy of Fallot with this unusual tricuspid anomaly rather than attempt one of several palliative procedures. In this case, however, it seemed unwise to carry out a Blalock-Taussig anastomosis because this would in no way relieve the suprasystemic pressure in the right ventricle. A Brock type procedure, relieving the infundibular stenosis, was theoretically satisfactory but carried with it the technical threat of removing too much infundibular stenosis and creating a large left to right shunt which might very well be poorly tolerated along with the tricuspid anomaly. When the anatomy was found to be borderline acceptable for a total repair it seemed wiser to expose the patient to the risk of total repair at this time, rather than to the combined risks indicated in the foregoing discussion.

The anomalous insertion of the septal leaflet of the tricuspid valve did not significantly interfere with the repair of the ventricular septal defect. It could be retracted to expose the area for placement of the sutures for the patch repair of the ventricular septal defect, as noted in the description of the operative repair. An outflow patch was not required; the opening seemed adequate and the dynamics of flow following cardiopulmonary bypass indicated a pressure difference of less than 20 mm. Hg over the annulus of the pulmonary valve. It seems very unlikely that



Fig 5 Angiocardiogram from right ventricle (A AP view B lateral view) shows domed stenotic pulmonic valve.

wedge-shaped infarcts in the upper and middle lobes of the right lung The right atrium was moderately d lated and the foramen ovale was closed The an terior and posterior leaflets of the tricuspid valve appeared delicate and translucent However the septal leaflet was markedly thickened and extended across the site of repair of the ventricular septal defect (Fig 6) Its base was located immediately below the right cu p of the aortic valve and appeared to insert just inferior to the aortic valve annulu in a manner described at operation (F g 7) The right ventricular myocard um showed a markedly in creased trabec lar pattern and hypertrophy mea ur ing 1 1 cm in thickness. The proximal portion of the pulmonary outflow tract was surgically widened and multiple small clots were adherent to the myocardial urface in this area. The infundibular portion of the right ventricle was narrowed by residual hy pertrophied muscle The valve tself was rudimentary being bicuspid only probe patent, and 1 0 cm. in circumference. The four pulmonary veins, left atrium left ventricle and mitral valves were unremarkable. The aorta was slightly to the right, which would have placed it over the interventric lar septum and right ventricle prior to surgical repair of the septal defect.

Histology of the lung revealed multiple areas of infarct as well as focal atelectasis The pulmonary arteries revealed minimal focal intimal thickening but there was no evidence of medial hypertrophy or elastification of the intima.

Discussion

The presence of a large ventricular septal defect in tetralogy of Fallot produces iden tical systolic pressure in the two ventricles. The occurrence of suprasystemic pressure in the right ventricle suggests the presence of either a very small ventricular septal defect or an intact ventricular septum with pulmonic valve stenosis. The presence of dominant a waves in the jugular veins together with marked right ventricular hypertrophy clinically as well as on the electrocardiogram were suggestive of an intact ventricular septum in the present case However the case with which the catheter could be passed through the ven tricular septal defect into the left ven tricle favored the presence of a large defect. It was felt that partial obstruction of the defect during systole could account for the severe hypertension in the right ventricle.

Anomalies of the tricuspid valve (Ebstein type) in severe pulmonary stenosis or atresia with an intact ventricular septum have been described[4,5] Congenital tri cuspid insufficiency (Ebstein type) has also been described in pulmonic valve stenosis with ventricular septal defect[6] Anomalous tricuspid valve in association with a ven tricular septal defect can simulate the features of pulmonic stenosis with intact ventricular septum[7] A similar mechanism could explain the unusua and

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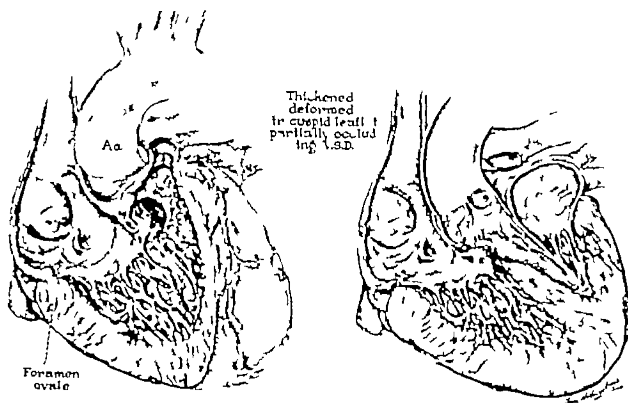


Fig. 7. Left. Sketch of the right side of heart as at operation showing at least partial occlusion of ventricular septal defect by thickened septal cusp of tricuspid valve. The foramen ovale was closed. Right. Sagittal view of heart showing relationship of septal cusp to ventricular septal defect and aortic outflow tract.

residual stenosis contributed significantly to her death. The intracardiac anomaly could be completely repaired and the tricuspid valve, though abnormally attached, did not present any difficulty in the repair.

The multiple infarcts in the lungs could be responsible to a large extent for the high pulmonary artery pressure recorded at the conclusion of the operation. It is possible that they were present before total correction and in the absence of any clinical evidence for pulmonary infarction they remained unsuspected. Additional operative and postoperative infarcts could not be excluded. The high pulmonary artery pressure could not have been secondary to any obstruction in the left side of the heart, such as an outflow narrowing or pulmonary venous stenosis, since the autopsy showed no such abnormalities. Under the circumstances described in this case, we feel that the cause of death was directly related to the pulmonary infarcts.

Summary

A $2^{3}/_{4}$ year-old girl with tetralogy of Fallot with suprasystemic pressure in the right ventricle has been described. The clinical findings of severe right ventricular dominance suggested an intact ventricular septum. At operation the septal leaflet of the tricuspid valve was attached unusually *high and aberrantly on the annulus* of the right ventricle, causing obstruction of the ventricular septal defect during systole. The literature has been reviewed and the pathophysiology of the lesion described. It is emphasized that it is possible to suspect the lesion clinically.

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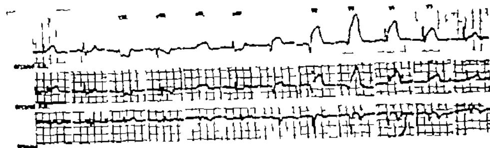


Fig. 1 ECG showing evol tionary changes typical of acute myocardial infarction.

360, respectively on the third day. All enzyme levels fell to within normal limits by the eighth day. The patient temperature was 102° F t its highest point on the second day and the white blood count (WBC) and neutrophilic percentage were 18,700 and 83 per cent, respectively on the third day. The blood sugar level on admission was 130 mg. per 100 ml. of blood. It dropped t normal on the second day and remained so throughout his hospital stay. Paper and cellulose serum electrophoresis revealed Type II hyperlipoproteinemia (Fredrickson classification). X-ray examination of the chest showed minimal left ventricular preponderance and prominent hilar shadows. Except for recurrent bouts of supraventricular tachycardia on the second and third day of hospitalization, the patient had an uneventful course and was discharged on Sept. 5 1969.

He had five subsequent admissions into the hospital, all for the same complaints and findings Dec. 4 to 13 1969 Jan. 13 to 26, 1970, Feb. 9 to 13 1970, Feb. 18 to 21, 1970 and April 10 to 14, 1970. Each hospital admission was because of the presence of chest pain increased by deep inspiration, dyspnea, tachycardia, and fever. During the first admission he was treated with aspirin but on all subsequent admissions he was treated with prednisone. This drug made him comfortable and abolished the fever within 24 to 36 hours. The subsequent recurrences were all precipitated by a decrease in the dose of prednisone below 40 mg. day. A pericardial friction rub was udible on each admission into the hospital.

All laboratory studies on each of the subsequent 5 admissions were negative except for WBC between 11,000 and 13,000 with normal dif ferential count, an absence of IgA, and slight elevation of alpha-2 globulin. IgG was 1,500 mg; IgM, 140 mg. and IgA, 0. The ECG showed increased nonspecific S-T segment and T wave abnormalities during the exacerbation which reverted to the pre-exacerbation pattern during remission.

The echocardiograms each admission revealed the presence of moderate amount of pericardial effusion with fluid demonstrated both anteriorly and posteriorly. The echocardiograms were normal before discharge from the hospital.

With each exacerbation the cardiac silhouett enlarged and subsequently returned to its previous size within eek of the institution of prednisone. A typical sequence of changes is shown in Fig. 2, A B and C.

During the second bout of the post-myocardial infarction syndrome, pericardial paracentesis was performed with the removal of approximately 400 ml. of slightly turbid yellow fluid. Cytologic examination of the fluid revealed almost exclusively neutrophilic polymorphonuclear leukocytes with a few mesothelial cells interspersed among them. The cell count was pproximately 95 per cent neutrophils with the rest endothelial cells (Fig. 3) The protein content was 4.3 Gm per 100 ml. of fluid. Electrophoresis of this fluid was reflection of the serum protein electrophoresis. Smears of the fluid were negative for infectious gents and cultures were discarded as sterile after 3 months of incubation. Viral studies were reported as negative. Fluorescent ANA, latex RA and lupus erythematosus (LE) and LE preparations were normal as were tudies of serum complements.

Discussion

There are surprisingly few reports on the histologic appearance of the pericardial fluid in Dressler s syndrome. The exudate is usually reported as grossly hemorrhagic.[5] However no distinction has been made between the gross appearance of fluid removed soon after the onset of an acute myocardial infarction and that removed much later. When the fluid is removed soon after the onset of an acute myocardial infarction it is not possible to be certain as to whether the grossly hemorrhagic fluid is due to the post-myocardial infarction syndrome or due to an extension of the infarction to the epicardial surface.

It is, therefore interesting to note that Dressler himself in his first report found straw-colored fluid resembling an exudate in a post-myocardial infarction syndrome 11 weeks after the onset of the illness. Unfortunately the fluid was not examined microscopically. It is also noteworthy that Dressler reported three instances of this syndrome with pleural effusion which was so large as to require aspiration. In two

Pericardial cellular response during the post myocardial infarction syndrome

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Dressler[1] was the first to report a series of patients with a febrile complication of recent myocardial infarction characterized by recurrent fever and pain of a pleural pericardial type with a striking tendency to recurrences This complication resembles idiopathic pericarditis Indeed the resemblance is so close that Faure and Cazeilles [2] who had previously reported a single incidence of this syndrome termed the illness idiopathic recurrent pericarditis and raised the question as to whether myocardial infarction might provide the ground for a virus infection supposed to be the cause of idiopathic pericarditis. Dressler suggested that the syndrome might represent a particular reaction to necrosis of the myocardium Itoh and his colleagues[3] have supplied immunologic data to support this concept Recently Burch and Colcolough[4] have suggested that this syndrome and postcardiotomy syndrome in general might be due not to a subsequent viral infection but rather due to activation of a latent viral infection

The character of the pericardial fluid might provide some insight into the nature of this disorder The fluid is usually described as hemorrhagic, but the description is in almost all instances based upon the naked eye appearance of the fluid Furthermore serosanguinous fluid is a common complication of acute myocardial infarction when the infarction extends to the epicardial surface It is, therefore possible for the pericardial fluid in Dressler s syndrome when aspirated within a short time after the onset of acute myocardial infarction to be contaminated with blood which is the result of the epicardial extension of the infarct. The pericardial fluid aspirated during an acute exacerbation remote in time from the onset of acute myocardial infarction is more likely to be characteristic of this syndrome

This communication reports on the character of the fluid in Dressler s syndrome which was aspirated 5 months after the onset of acute myocardial infarction

Case report

I P a 35-year-old man, was admitted into the Temple University Hospital for the first time on Aug 12 1969 because of the abrupt onset of severe retrosternal pain and profuse perspiration. He had had vague chest pain for 2 days before admission but before that time had regarded himself as well and played tennis and basketball up to the weekend before admission into the hospital A clinical diagnosis of acute myocardial infarction was made and confirmed by typical evolutionary changes in the electrocardiograms (FCG s) (Fig 1) and by typical changes in the levels of enzymes in the blood. The creatine phosphokinase activity (CPK) peaked on the second day to 429 and the serum glutamic oxalacetic transaminase (SGOT) and serum lactic dehydrogenase (LDH) to 1 472 and

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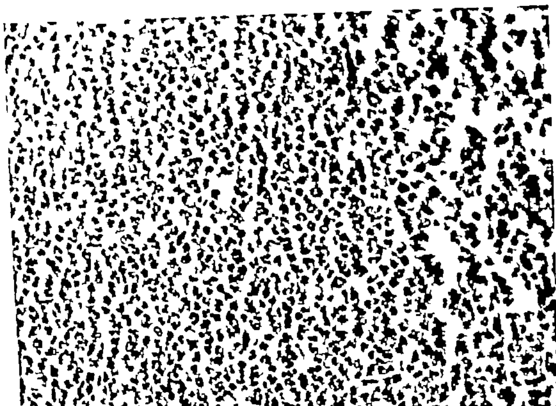


Fig. 3. Cytological study performed during second bout of myocardial infarction.

ent, probably because the virus directly involves the bone marrow and peripheral leukocytes. On the other hand respiroviruses which do not characteristically produce viremia are associated with leukocytosis, and the increase in white cells is particularly prominent at the site of tissue destruction. A neutrophilic response is, therefore not inconsistent with the hypothesis of a viral infection as a cause for this syndrome nor is the clinical course. Andrews has spoken of the unlucky few who become clinically sick with a viral infection and who develop an activation of a latent viral infection when exposed to a variety of stresses, a concept applied to the postcardiotomy syndrome by Burch and Colcolough.

Finally the characteristic recurrent clinical syndrome after myocardial infarction is rarely a problem of diagnosis. The first clinical bout almost always is a problem—or should be—because there is no specific laboratory test diagnostic of this syndrome. It is important to exclude other specific causes of pericarditis by a variety of cultural and immunologic studies as well as to exclude pulmonary and pleural diseases. The finding of neutrophilic leukocytes in the aspirate of the pericardial fluid might lead to suspicion of a bacterial suppurative pericarditis. This disorder was a common complication of septicemia and contiguous pulmonary and pleural suppuration in the preantibiotic era. Today this complication occurs rarely and can follow acute myocardial infarction. In contrast to the post-myocardial infarction syndrome in which the patient looks relatively well in spite of the presence of severe pain patients with bacterial suppurative pericarditis are obviously sick and toxic and not infrequently have signs of pericardial tamponade. The disorder is fatal unless recognized early and treated with appropriate antibiotics and if necessary surgical drainage. The aspirate in bacterial suppurative pericarditis is grossly purulent in contrast to the fluid in

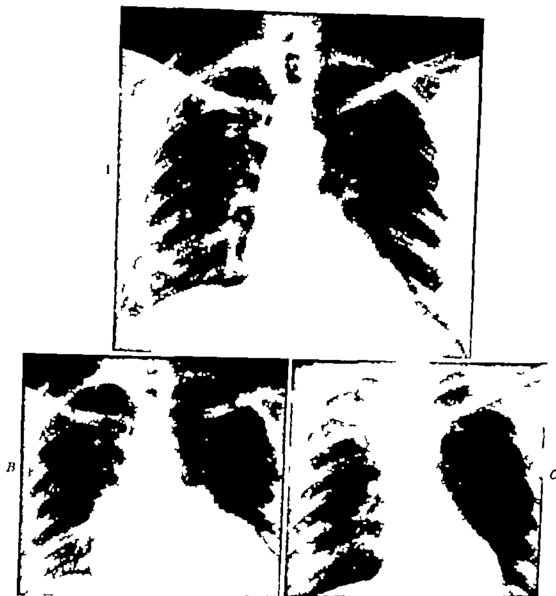


Fig. 2. Sequence of changes in cardiac silhouette. 1, Dec. 18, 1969. B, Jan. 13, 1970. C, Jan. 26, 1970.

instances the fluid was straw colored; in one hemorrhagic. The possibility that anticoagulant therapy could have contributed to this last case, he stated, should be taken into consideration.[1] Unfortunately, again the fluid was not examined microscopically. Finally, Dressler[4] reported a flare up of pericarditis complicating myocardial infarction after 2 years of steroid therapy. In this instance a microscopic examination of fluid was made and its cellular content was composed almost exclusively of neutrophilic polymorphonuclear leukocytes, a finding identical with that of the present case.

Unfortunately, nowhere does Dressler discuss this microscopic finding nor does he discuss the possible significance of the finding in contrast to the usual reports of hemorrhagic pericardial effusion in this syndrome. It is therefore not surprising that the pericardial neutrophilic response in this syndrome has been buried in his case report and has, to my knowledge, been neither mentioned nor discussed in subsequent articles on this syndrome or in textbooks of cardiology.

Why this syndrome is, at least at times, associated with a neutrophilic response is not clear. One would anticipate an eosinophilic response if the theory of hypersensitivity were correct. On the other hand, viral infections are usually associated with leukopenia. However, Portnoy and his associates[7] have shown that viral infections produce leukopenia only if viremia is pres-

Clinical pathologic conference

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Clinical abstract

A 28-year-old Caucasian woman developed exertional dyspnea in May 1969 during the fifth month of her seventh pregnancy The symptoms did not progress and pparently ceased after a normal delivery of viable male infant in August, 1969 The shortness of breath disappeared but two weeks later she again noted dyspnea on exertion. The symptoms progressed so that she was unable to dress herself without becoming short of breath however there was no orthopnea. She was admitted to nother hospital with severe dyspnea following an episode of dizziness and diaphoresis. The electrocardiogram (ECG) showed T-wave inversion in Leads V to V ith a normal QRS axis. The chest film, lung scan, and enzymes were normal. She was discharged without medication on a regimen of limited activity

Dyspnea persisted for the next month. Six days prior t admission here she again became dizzy diaphoretic, and very weak and was readmitted to the local hospital. Blood pressure t that time was 110/100. The ECG again showed T-wave inversion in the precordial leads. Serial chest films were normal. There was no history of chest pain or hemoptysis. Digoxin was started. She remained in stable condition but five days later on Oct. 13, 1969 she became very weak and diaphoretic without detectable peripheral pulses or blood pressure, lthough she was alert and had normal sinus rhythm. Intravenous Levophed was started and the patient was transferred to Presbyterian-St. Luke' Hospital.

On admission, she was afebrile with regular heart rate of 100 per minute and respirations of 22 per minute. The blood pressure was not obtainable. Peripheral pulses were absent and the extremities were cold nd violaceous in color The lungs were clear A slight right ventricular heave, but no cardiomegaly was described. The S_1 and S_2 were normal. A Grade 2/6 systolic ejection murmur was heard along the lower left sternal border S_3 and S_4 gallops were present. The P was split. The veins of the neck were mildly distended and smooth, nontender liver was palpated one finger breadth below the costal margin. The spleen was not palpated, and there was no tenderness of the lower legs. At this time the blood pH was 7 46 and the blood gases were as follows. pCO_2 22 mm. Hg pO 64 mm. Hg w th O saturation of 92.2 per cent and base excess of −6. Angiocardiographic tudies showed a normal inferior vena cava, right trium, left trium, left ventricle, and aorta. The ight ventricle and proximal pulmonary arteries ere dilated, but no clear occlusive clots were seen. The pressures recorded wer right ventricle, 80/20- pulmonary artery 80/30- right trium, 11 ith wedge of 9 mm. Hg It was decided that the patient had pulmonary emboli and, on the second hospital day the inferior vena cava was ligated. Postoperatively the central venous pressure was 2 to 3 cm. of H_2O and the blood pressure had to be maintained with Isoprel. She was given heparin. Lasix was used to maintain urinary output. On the next day her temperature was 103.8° F and the central venous pressure 19 cm. of H_2O. Cultures of blood and urine showed no growth and cultures of sputum were unremarkable. Penicillin coverage was instituted and the temperature dropped to 100° F On the fourth day with 6 L. per minute of O_2 given by nasal cannula, the blood gases were as follows pH 7 42 pCO_2, 29.3 mm. Hg pO_2, 86 mm. Hg with the per cent of O_2 saturation t 96.3 base excess was −3.9 mEq. per liter On the twelfth hospital day the patient had cardiopulmonary arrest and was resuscitated, but three hours later she died.

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Dressler's syndrome in which the fluid is slightly turbid and only microscopically suppurative

Summary

A case of post-myocardial infarction syndrome is reported in which fluid was aspirated months after the onset of acute myocardial infarction The fluid was suppurative composed almost exclusively of neutrophilic polymorphonuclear leukocytes. It is suggested that this response might be characteristic of this syndrome and that previous reports of a serosanguineous reaction might be due to contamination with blood from epicardial extension of the acute myocardial infarction

Addendum

The patient as yet (2/11/71) has not been able to discontinue prednisone for more than three weeks without developing clinical exacerbation of the post-myocardial infarction syndrome

I wish to thank Sumitra Subbarao M D., a resident in pathology for the photomicrograph

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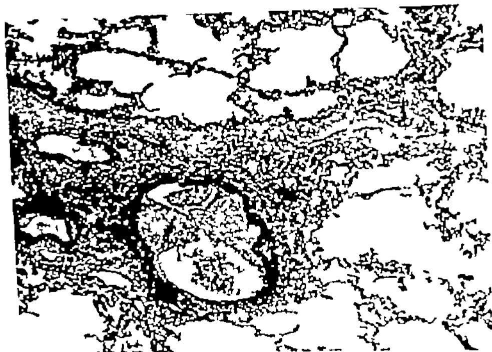


Fig. 3. Section of lung with marked lobular septal thickening and partial occlusion of medium-sized vein. (Verhoeff' elastic stain. ×50.)

redistribution pattern or Kerley B lines indicative of pulmonary venous hypertension are apparent. There is bilateral pleural effusion. The platelike densities persist until the day antemortem when they clear In summary the pattern is that of pulmonary interstitial edema and pulmonary venous overfilling with pleural effusion There is no evidence of pulmonary hypertension progressive cardiac enlargement or chronic pulmonary venous hypertension. The absence of pulmonary artery hypertension and atelectatic areas makes the possibility of multiple pulmonary emboli less likely A chronic cardiac disorder is less likely because of the absence of typical signs of pulmonary venous hypertension. The pattern then best fits with some failure of the myocardium of an acute nature or with some failure of a normal pulmonary venous return. The age of the patient makes myocardial infarction unlikely There is no history of fluid overload The possibilities of pulmonary venous occlusions due to some clotting disorder or myocarditis resulting in the failure of the heart cannot be excluded

DR. R. L. HUGHES Thank you The radiographs here support her symptomatology but not her physical or catheterization findings. Because of the rapid course I am going to be somewhat arbitrary in my discussion. I feel this woman's illness must have resided in her lungs, and I shall choose to break the discussion into those diseases which occur downstream within or upstream of the alveoli. Although her ECG changes are compatible with myocarditis I am going to exclude that diagnosis on the basis of normal heart size Other downstream entities which should be considered such as mitral stenosis or myxoma can be excluded by the normal wedge and the time course. Those diseases which affect primarily the veins, such as primary pulmonary venous thrombosis, with or without angiitis primary pulmonary venous sclerosis, coarctation or granulomatous venous disease are certainly considerations, particularly with the x-ray findings. The absence of râles during either hospital course and normal chest x-rays until just prior to her death when her disease was well-established would tend to point away from these diagnoses. Widespread pulmonary venous disease frequently gives a



Fig. 1 Admission film.



Fig. 2 Portable chest film 3 days before death.

The admitting hemogram showed a hemoglobin of 11 1 Gm per cent hematocrit 34 8 per cent leukocytes, 9 400 with a differential of 52 polymorphonuclear leukocytes, 18 band forms, 25 lymphocytes, 5 monocytes, and 115 000 platelet The red blood cell mass was 16.1 ml plasma volume 28 7 ml. nd blood volume 44 8 ml. per kilogram of body weight The mean corpuscular volume was 102 mμ mean corpuscular hemoglobin, 32 4 μμg mean corpuscular hemoglobin concentration 31 9 Gm. per cent The urinalysis, serum electrolytes, blood urea nitrogen glucose and bilirubin were within normal limits. The serum glutamic oxaloacetic transaminase (SGOT) was 145 unit the serum glutamic pyruvic transaminase (SGPT) 185 isocitric dehydrogenase (ICD) 2 140 and lactic acid dehydrogenase (LDH) 1 080 Postoperatively the SGOT wa 200 ICD 3,500 and LDH 3 250 u its. The uric acid was 14 1 mg per cent. The latex fixat on t ter w 1 1 280 and the C' reactive protein was 4+ The nt nucle r antibody t ter was nder 1 10

Discussion

DR R L. HUGHES This 28 year-old woman developed an illness which progressed inexorably to her death over a 2 month period Her principal symptoms were progressive dyspnea and intermittent episodes of dizziness and diaphoresis

Following admission here when she was desperately ill she was apparently not septic and an emergency angiogram did not reveal any major obstruction or thrombosis An extraperitoneal inferior vena cava ligation was done without complication and she was heparinized She developed a fever postoperatively and on the fifth hospital day sustained a cardiorespiratory arrest was resuscitated but could not be subsequently revived

Perhaps at this time it would be appropriate to review the chest films.

DR JOHN T ENGLISH The admission chest film (Fig 1) shows the heart at the upper limits of normal size Pulmonary vasculature is not distended There are several horizontal linear densities widely scattered in the upper half of the right lung These are of unknown significance These have been called areas of platelike atelectasis or thickened areas of lung interstitium The central venous catheter lies at the junction of the superior vena cava with the right atrium and electrocardiographic leads are in place

Six subsequent portable radiographs were taken over the next 5 days and all show the same basic pattern with minor fluctuations Fig 2 is a film of Oct. 15 1969 taken three days antemortem which is representative of the group The heart has not enlarged There is an over-all grayness of the lung fields, an increase in pulmonary vascular markings and a smudging of their margins. These signs are indicative of interstitial edema No

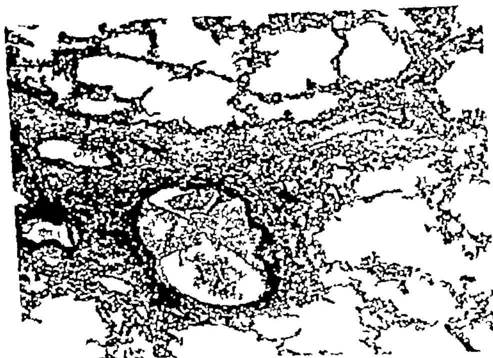


Fig. 3. Section of lung with marked lobular septal thickening and partial occlusion of medium-sized vein. (Verhoeff' elastic stain. X50.)

redistribution pattern or Kerley B lines indicative of pulmonary venous hypertension are apparent. There is bilateral pleural effusion. The platelike densities persist until the day antemortem when they clear. In summary, the pattern is that of pulmonary interstitial edema and pulmonary venous overfilling with pleural effusion. There is no evidence of pulmonary hypertension, progressive cardiac enlargement, or chronic pulmonary venous hypertension. The absence of pulmonary artery hypertension and atelectatic areas makes the possibility of multiple pulmonary emboli less likely. A chronic cardiac disorder is less likely because of the absence of typical signs of pulmonary venous hypertension. The pattern then best fits with some failure of the myocardium of an acute nature or with some failure of a normal pulmonary venous return. The age of the patient makes myocardial infarction unlikely. There is no history of fluid overload. The possibilities of pulmonary venous occlusions due to some clotting disorder or myocarditis resulting in the failure of the heart cannot be excluded.

DR. E. L. HUGHES. Thank you. The radiographs here support her symptomatology but not her physical or catheterization findings. Because of the rapid course, I am going to be somewhat arbitrary in my discussion. I feel this woman's illness must have resided in her lungs, and I shall choose to break the discussion into those diseases which occur downstream, within, or upstream of the alveoli. Although her ECG changes are compatible with myocarditis, I am going to exclude that diagnosis on the basis of normal heart size. Other "downstream" entities which should be considered, such as mitral stenosis or myxoma, can be excluded by the normal wedge and the time course. Those diseases which affect primarily the veins, such as primary pulmonary venous thrombosis, with or without angiitis, primary pulmonary venous sclerosis, coarctation, or granulomatous venous disease are certainly considerations, particularly with the x-ray findings. The absence of râles during either hospital course and normal chest x rays until just prior to her death when her disease was well-established would tend to point away from these diagnoses. Widespread pulmonary venous disease frequently gives a

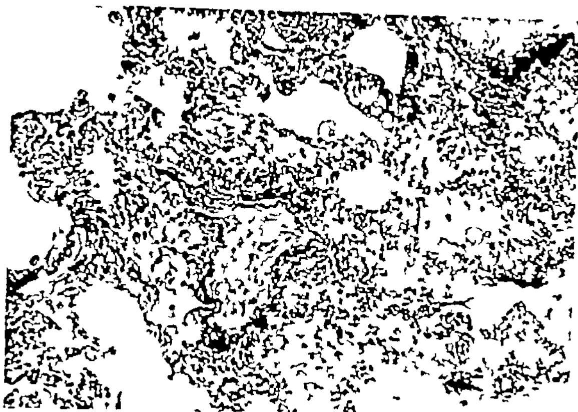


Fig. 4. A small almost occluded pulmonary vein (arrow). (Verhoeff's elastic stain. X130.)

wedge tracing very similar to that seen in the more proximal pulmonary arteries. The presence of a normal tracing and a normal wedge pressure tend to support this exclusion.

Most diseases which occur within the alveoli would fall into an infiltrative classification. Any granulomatous disease including sarcoidosis and tuberculosis could be responsible for pulmonary hypertension. However, there is very little evidence to support these entities. The time course is consistent with that of Hamman Rich syndrome but the negative x rays until this admission would tend to exclude it. Eosinophilic granuloma and Liebow's desquamative interstitial pneumonia[1] would likewise not be considerations. The third category of disease which might occur within the alveolus is neoplastic. I am reluctant to exclude this possibility. Lymphangitis carcinomatosis can prove fatal within two months. Of various tumors which might embolize to the lungs, those of hematopoietic origin and lymphomas must head the list and could well go undetected in such an ill patient. To my mind the elevated uric acid would support such a possibility as would the continued deterioration following her inferior vena cava ligation. The x ray sequence is compatible with such a diagnosis, and I put this consideration high on my list.

Those diseases occurring primarily upstream of the alveoli include such entities as carcinoid syndrome, polycythemia, fat embolism, and parasitic infestations but there is little clinical support for such illnesses. Causes for arteritis need to be considered. Did this lady have an arteritis either necrotizing or nodular? This, too, is difficult to exclude. The elevated uric acid, the mild liver abnormalities, the latex fixation, C reactive protein, and the time course are all compatible. The patient, however, was nonallergic. She had a normal protein electrophoresis and a normal sedimentation rate on admission and her renal function was normal. The normal antinuclear antibodies do not, unfortunately, exclude such a diagnosis. Like many other entities, an autoimmune angiitis remains a distinct possibility.

Among the final entities that I will be discussing this afternoon, recurrent pulmonary emboli and primary pulmonary hypertension are highest on my list. In my view these two diseases are inextricably entwined in most pathologists' views, and clinicians also have difficulty in separating

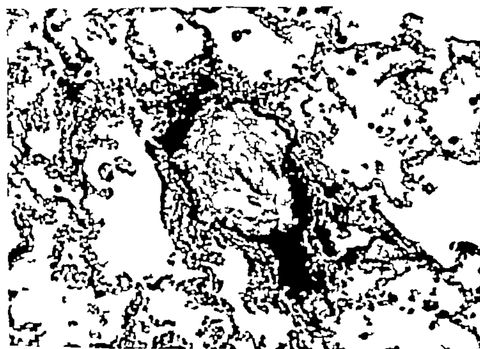


Fig. 3 Fibrous occlusion of a small pulmonary vein. (Verhoeff' elastic tain. ×130.)

them. Both can be associated with dry lungs and x-ray pictures suggestive of pulmonary edema. Pulmonary emboli may well be the most common of all pulmonary diseases. Common diseases occur commonly except in clinical pathologic conferences, but I believe there is strong evidence to support this diagnosis. The patient had 7 children. It is well recognized that many patients sustain massive pulmonary emboli with signs absent in the legs and on x-ray. In addition, as many as 85 per cent of all emboli probably occur in vessels less than 1 mm in diameter, so that a negative angiogram may be of little help. The fact that the patient deteriorated after an inferior vena caval ligation and anticoagulation therapy is somewhat against the diagnosis, but post-ligation emboli do occur and I find it very difficult not to consider this possibility. This brings me to the last consideration where I will hang my hat. Primary pulmonary hypertension has been described as a disease of neurotic young females. It is a disease of unknown etiology and frequently occurs in women who have recently been pregnant, supporting a hypothesis that the disease may be due, in part, to amniotic fluid emboli. It is usually rapidly fatal with death occurring within an average of 1 to 2 years after the onset of symptoms. However, cases have been described with courses as short as 6 weeks and as long as 15 years. It occurs four times as commonly in women as in men and is characterized by the classic triad of dyspnea on exertion, syncope, and substernal chest pain, the so-called hypercyanotic angina.[4] This latter term, though descriptive of patients with severe disease, is probably inappropriate as cyanosis is not a common manifestation of this entity. These patients less commonly suffer from peripheral edema and orthopnea, but as part of the syncopal episodes, they frequently sustain recurrent dizzy spells. Cough and palpitations, hoarseness, hemoptysis, and Raynaud's phenomenon have all been described but are rare. Many of these young women suffer from psychoneuroses, and psychotic episodes have been described. The physical findings in this disease are quite similar to the ones in this case. Unfortunately, they are only a nonspecific reflection of pulmonary hypertension and are not of diagnostic significance. These patients are almost always hypotensive, have a booming second cardiac sound, a frequent summation gallop, increased heart size, and ne-

sternal heave Murmurs of tricuspid in sufficiency or a pulmonary ejection murmur with or without a click are sometimes heard Many of these patients perhaps as many as 75 per cent suffer from arterial desaturation The mechanism of action of this is not well understood at the moment and hypotheses ranging from diffusion de fects to VQ abnormalities have been con structed Cyanosis clubbing and throm boses are rare in this disorder as in the occurrence of frank pulmonary edema again an unexpected and to me unex plained complication

Pathologically recurrent pulmonary em boli and primary pulmonary hypertension may be identical with a proliferation or thickening of one or all layers of the pul monary arterioles Therapy for most of these entities is quite frustrating Both oxygen and use of intravenous alpha block ing drugs may temporarily lower the pul monary artery pressure[7] Oral therapy however is disappointing and we are presently left with continuous oxygen and supportive measures for sustaining these patients

In conclusion I feel that this lady suf fered from primary pulmonary hyper tension Whether this was due to a primary process or secondarily to recurrent small emboli may be difficult to distinguish but I predict that multiple arterioles occluded by subintimal thickening will be found I cannot exclude either a necrotizing ar teritis or carcinomatosis, but I would not place either of these first on the list It will be most interesting to see what Dr Dainauskas tells us.

Autopsy findings

DR JOHN R DAINAUSKAS At autopsy the patient s heart was very slightly enlarged (325 grams) and a small apical scar was seen in the right ventricle The lungs were increased in weight (900 grams) reddish white mottled in appearance and rubbery in consistency A small amount of edema fluid was expressed from the cut surfaces. The major arteries and veins were patent without evidence of embolization Bilateral pleural effusions (500 c c total) were pres ent and changes of chronic passive conges tion were apparent in the liver

Microscopically the medium sized and small pulmonary veins as well as venules were the site of a conspicuous obliterative process. The lumina of many of these vessels were completely or almost com pletely obliterated by loose proliferating connective tissue The lesions were wide spread and not confined to any particular section of the lungs. Smooth muscle hyper plasia of the vessel walls was not impres sive Occasional veins had several small channels indicative of recanalized thrombi. However there were no recent or organiz ing thrombi and no evidence of phlebitis. The major large veins were patent and neither grossly nor microscopically was there any evidence of obstruction in these vessels. The pulmonary arterioles had a moderate degree of medial hypertrophy and fibrosis None was occluded There was no evidence of an arteritis. Small deposits of hemosiderin-containing macrophages and a few multinucleated giant cells were pres ent This lesion in pulmonary veins has been called pulmonary venoocclusive dis ease and about a dozen cases have been reported Most writers credit Hora[8] with being first to report this lesion An oblitera tive sclerosing process of small pulmonary veins is the common lesion The process is generally believed to represent a throm bosis although only in a few cases have actual thrombi been demonstrated The lesion usually is confined to pulmonary veins as in this case without involvement of systemic veins.

Severe venous intimal fibrosis has been described[9] associated with high pulmonary blood flow that occurs with atrial septal defect Thrombosis of small pulmonary veins can occur with acquired or congenital obstruction of main pulmonary veins, but none were obstructed in this case.

Weisser and associates,[10] in a description of pulmonary venoocclusive disease in a 15 year-old girl drew an analogy between the obliterative lesions of the pulmonary veins and obliteration of intrahepatic veins in the Budd Chiari syndrome In Jamaica and South Africa the liver disease has been shown to be caused by Senecio alkaloids contained in certain bush teas The similarity of the obliterative process in the pulmonary veins and the hepatic lesions raises the question as to whether the pul monary venoocclusive disease could be

due to a toxic agent, possibly inhaled

One of our patient's infants died at the age of 8 months after an attempt to repair a congenital malformation of the heart. The infant had stenosis of the right pulmonary veins and patent ductus arteriosus. It is interesting to note that 3 of 4 children of a patient with pulmonary venoocclusive disease reported by Heath and co-workers[11] died with cyanotic congenital heart disease.

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Disorders of hemoglobin-oxygen release in ischemic heart disease

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The emergence of ischemic heart disease as the most frequent and varied problem confronting today's cardiologist has contributed to the evolution and development of new concepts of approach to this entity. The time-honored view of obstructive coronary disease as the *sine qua non* of myocardial ischemia and infarction has of necessity been qualified by the recognition of these phenomena in the presence of patent coronary vasculature. The approach discussed herein is derived from a consideration of the multifactorial influences balancing myocardial oxygen supply with demand as illustrated in the excellent review of the subject by Haddy.[1] Obviously circulatory integrity and myocardial tissue demands are basic to this scheme. A third critical factor that of oxygen transport between blood and tissue has recently been brought into sharper focus and it is the intent of this paper to discuss developments in this area and to place them in their proper clinical perspective.

Dysfunction of the blood-oxygen transport system was described by Astrup[2] in 1964 in a series of patients with Buerger's disease. In 1965 anomalous hemoglobin oxygen dissociation curves were demonstrated by Mizukami and Eliot[3] in a group of premenopausal women with unequivocal evidence of myocardial ischemia and/or necrosis despite normal coronary arteriograms. Postmortem examination of three of these women revealed subendocardial infarction in the absence of large or small vessel disease. Sidd, Kemp, and Gorlin[4] have recently reported transmural infarction in a young man with patent coronary vasculature.

Additionally, numerous investigators have noted ischemia or infarction in both sexes with angiographic evidence or autopsy confirmation of patent coronary vasculature.[5-7] Recent interest has been centered about the possible role of abnormal blood-oxygen transport in tissue oxygenation.[8,9]

Biophysical considerations

An understanding of blood-oxygen transport presupposes a foundation in the mechanisms of the hemoglobin-oxygen interac

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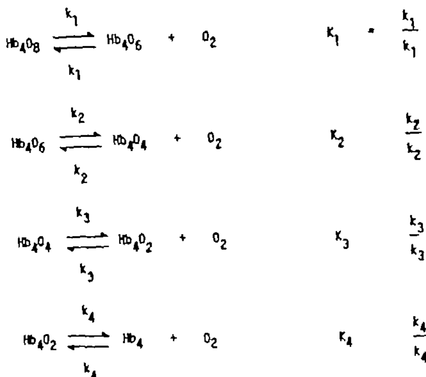


Fig 1 Adair four-step hypothesis written in terms of four dissociation equilibrium reactions. The large K's represent dissociation equilibrium constants for each hemoglobi subunit (K_1, K K_3, K_4) The small k are the associated kinetic release (k k k_3, k_4) and binding (k k k k ') constants.

tion. Excellent detailed reviews of this subject may be found elsewhere [4-13] Basically the hemoglobin molecule consists of two types of polypeptide chains, each chain containing one heme prosthetic group (iron-porphyrin ring) The two chains are differentiated according to their amino acid composition and are designated α and β respectively One adult hemoglobin molecule consists of two α chains and two β chains and is given the formula $\alpha_2\beta$ The heme prosthetic groups of each chain are capable of binding and releasing one molecule of oxygen. The exact mechanism by which hemoglobin binds and releases oxygen remains debatable. There is evidence supporting the view that each α-β chain dimer acts as the main functional unit in hemoglobin s interaction with heme ligands such as oxygen.[14] Another school presents evidence to support the tetrameric form as the basic functional unit.[13] In the ensuing discussion, we shall employ the latter hypothesis. The sequential binding and release of oxygen by each subunit (one heme and one polypeptide chain) influences the binding and release at each remaining subunit. The sigmoid nature of the hemoglobin-oxygen equilibrium curve has been attributed to this phenomenon, commonly termed heme heme interaction Thus in considering the hemoglobin-oxygen equilibrium reaction one must deal with the number of rate or kinetic, constants that express the separate reactions of binding and release of oxygen at the four separate sites on the hemoglobin molecule adopting the model of Adair[14] (Fig 1) The hemoglobin-oxygen equilibrium curve may be represented by an over-all dissociation equilibrium constant, which is in turn *derived from* the ratio of the several kinetic "off" (release) *constants to the several kinetic* on (binding) constants. (For the purpose of this discussion, such a simplified representation will suffice.) Obviously changes in this ratio may be due to alterations in either the rate of release or of binding of oxygen, or both, resulting in shifts of the

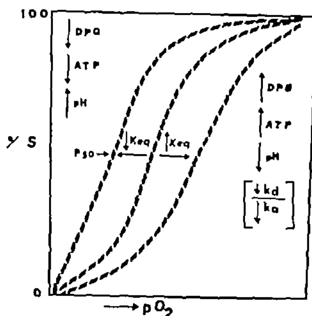


Fig. 2. The hemoglobin-oxygen equilibrium curve and the influence of some known affectors. Per cent saturation of hemoglobin (%S) is plotted against pO_2. P_{50} is the half-saturation point for hemoglobin. *Keq* is the over-all dissociation equilibrium constant. k_d is the over-all constant for oxygen release; k_a is the over-all constant for oxygen binding. The paradox of a rightward shift in the equilibrium curve with a decreased rate of oxygen release is illustrated in brackets.

equilibrium curve in either direction. It cannot be determined then whether a shift of the curve is due to (1) an altered rate of release of oxygen, (2) an altered rate of binding of oxygen, or (3) both, unless the over-all kinetic constant for at least one of these functions is determined. Support for this concept is found in a recent report by Klocke, Bauer, and Forster[17] which indicated that shifts in the equilibrium data in their study could not be attributed solely to changes in the rate constants for the release of oxygen.

A number of conditions are known to alter the hemoglobin-oxygen equilibrium curve. The clinically important ones have recently been reviewed in detail by Bunn and Jandl.[18] The equilibrium curve for the hemoglobin-oxygen interaction is characterized by two parameters. These are the P_{50} (partial pressure of oxygen at which 50 per cent of the hemoglobin is saturated) and by Hill's constant *n*, which is an empirical number qualitatively representing the degree of sigmoidness of the equilibrium curve. Major affectors of the equilibrium curve which are of physiologic importance are 2,3-diphosphoglycerate (2,3-DPG), adenosine triphosphate (ATP), and pH. ATP and 2,3-DPG are present in the red blood cell coincident with the cell's glycolytic metabolism, the former existing normally at a molar ratio approximately equal to the concentration of hemoglobin, the latter at lower levels.[19] It has been demonstrated that elevations in 2,3-DPG and/or ATP shift the equilibrium curve to the right (higher P_{50}) as does a decrease in pH.[20,21] Conversely, decreased 2,3-DPG and/or ATP levels as well as elevated pH cause the curve to shift to the left (lower P_{50}) (Fig. 2). Changes in levels of these affectors and their influence on the hemoglobin-oxygen equilibrium curve have recently come into sharper focus due to the various clinical settings in which the levels are altered. These include chronic obstructive pulmonary disease, cyanotic congenital heart disease, anemia, and hypoxia due to high altitude.[22-24]

ATP, 2,3-DPG, and pH also exert an effect on the actual rate of release of oxygen from hemoglobin. Evidence that purified solutions of human adult hemoglobin release oxygen faster in the presence of 2,3-DPG has been presented by Salhany, Eliot, and Mizukami.[25] These results have recently been confirmed.[17,26] It has been known for some time that a decrease in pH is associated with an increased rate of oxygen release.[27,28]

Clinical models

Abnormalities of hemoglobin-oxygen transport may be inherent or acquired as will be subsequently illustrated.

An inherent model that exhibits the distinction between equilibrium and kinetics information and the importance of oxygen release kinetics is sickle hemoglobin (hemoglobin S). In both the heterozygous and homozygous forms, sickle cell disease has been associated with ischemic infarctions in diffusely scattered organs often in the absence of vascular occlusions. This observation raises the question of abnormal oxygen release from hemoglobin S.

The whole blood equilibrium curve in sickle cell disease is known to be shifted to the right relative to normal, implying a lower oxygen affinity.[29] It has been pointed

out that this shift to the right may be in part, a result of the molecular aggregation of deoxygenated sickle hemoglobin.[20] Such aggregation would of course favor the deoxygenated form at equilibrium resulting in the rightward shift of the curve. With this in mind, one is faced with the question of the state of oxygen release by hemoglobin S. Study of the kinetics of oxygen dissociation should allow observation of that component of the oxygen interaction almost free of the influence of aggregation. Since oxygen dissociation is proposed to precede the deoxygenated aggregated state such a distinction is warranted and necessary.

When the over-all rate of oxygen release from purified (free of organic phosphates) isolated sickle cell hemoglobin was directly measured the rate of deoxygenation was 22 per cent lower than that of purified isolated hemoglobin A[31] (Table I). On the other hand hemoglobin-oxygen equilibrium measurements fail to reveal a significant difference between purified sickle and adult hemoglobin, regardless of the presence of 2,3-DPG.[22] The kinetic results however illustrate that hemoglobin S releases oxygen slower not only in the isolated form but also in the presence of comparable amounts of 2,3-DPG. While the relative responsiveness to 2,3-DPG of the two hemoglobins is the same (per cent change in k_4 due to 2,3-DPG for hemoglobin A is 58.0 ± 1.6 per cent and for hemoglobin S 59.0 ± 1.2 per cent) an absolute difference persists at each incremental step.

In order to understand the decreased rate of oxygen release in the face of no shift in the equilibrium curve in hemoglobin S solution it is necessary to assume that the rate of oxygen binding is decreased relative to hemoglobin A. These kinetic abnormalities of isolated hemoglobin S may be accounted for by some intrinsic structural property of hemoglobin S. The structural basis for this behavior may be the *intramolecular* interactions proposed by Murayama,[23] as distinguished from the *intermolecular* interaction proposed to account for the aggregation of deoxygenated hemoglobin S. Thus, decreases in the rates of both oxygen binding and release may well combine to result in the observed normal position of the equilibrium curve of hemoglobin S *in solution*. In the red cell the formation of linear aggregates of deoxygenated hemoglobin S should further decrease the rate of oxygenation masking the decreased rate of release by shifting the whole blood oxygen-equilibrium curve to the right.

*Table I. Over-all rate constant for oxygen release (k_4) and P_{50} data for isolated purified adult (A) and sickle (S) hemoglobin (Hb) in the presence and absence of DPG**

Hb	k_4 ($sec.^{-1}$)		P_{50} (mm. Hg)	
	With DPG	Without DPG	With DPG	Without DPG
A	50.9	32.1	1.83	1.27
S	39.5	24.8	2.17	1.36

*P_{50} data were taken from paper by Bunn and Briehl.[22] Kinetic data are from Salhany, Mizukami, and Eliot.[31] Kinetics were performed on 0.02 mM. hemoglobin concentrations in 0.05 M TRIS-HCl, pH 7.0, at 25° C, in the absence of 2,3-DPG and with 0.2 mM. 2,3-DPG according to the methods of Salhany, Eliot, and Mizukami.[20]

The demonstration of significantly elevated levels of 2,3-DPG in patients with sickle cell disease[34]—perhaps as a consequence of anemia—illustrates a molecular compensatory mechanism that may be operative to meet normal tissue needs. However at the limit of oxygen demand the decreased rate of oxygen release may contribute to tissue ischemia. These observations illustrate that concepts derived from equilibrium data alone are inadequate to represent the true dynamic state of the hemoglobin-oxygen interaction.

An acquired model of hemoglobin-oxygen dysfunction is found in animals and man in whom carbon monoxide intoxication is associated with myocardial ischemia hemorrhage or necrosis in the absence of vascular occlusion.[35,36] The rate of oxygen release from hemoglobin which has 50 per cent carbon monoxide bound is considerably slower than that from hemoglobin unbound to carbon monoxide.[37] It has been suggested that carbon monoxide binds to hemoglobin on a cell-to-cell basis, rather than distributing proportionately

and evenly throughout the hemoglobin mass of the red cell population.[38] This blood then would represent a chemical anemia in the form of packages of red blood cells laden with carboxyhemoglobin on which few sites remain for oxygen binding and from which the remaining oxygen molecules are released slowly. Carboxyhemoglobin levels of 6 to 20 per cent may be acquired by cigarette smoking.[39] Carbon monoxide may also directly compromise the cytochrome system.

A third incompletely characterized model of hemoglobin-oxygen dysfunction has been found in some relatively young patients with normal coronary arteries and objective signs of myocardial ischemia or infarction.[8,40,41] As previously noted, these patients have not shown evidence of large or small coronary artery disease at necropsy. Hemoglobin-oxygen equilibrium curves performed on the hemoglobin of these patients demonstrated a shift to the right, i.e., decreased affinity. Recently Vokonas and associates[42] have reported 13 patients with anginal pain, normal hemodynamic data, and normal coronary arteries demonstrated by selective cinearteriography. Three of these patients had objective evidence of ischemia. These patients were found to have normal whole blood-oxygen equilibrium curves with normal levels of 2,3-DPG. These results are not surprising when viewed considering the above discussion of the interpretation of equilibrium data. Normal oxygen equilibrium curves are certainly possible at the whole blood level where many other factors determine its position. However, normal whole blood-oxygen equilibrium curves do not eliminate the possibility of slow oxygen release from the blood of these patients. Deoxygenation kinetics may be assayed at the hemoglobin[39,42,43] or whole blood[43,44] levels.

Recently two men and two women of the above type were studied with the use of techniques for measuring the rate of release of oxygen from hemoglobin.[47] The kinetic studies were initially performed on membrane-free hemolysates of four apparently healthy nonsmoking individuals as well as on the patients. No attempt was made to remove 2,3-DPG or ATP. The results of the deoxygenation kinetics for the unpurified hemolysates of the normal individuals and the patients demonstrated that the pseudo-first order rate constant for deoxygenation between 85 and 40 per cent saturation (expressed herein as either k_d or k_{444}) was found to be 33.4 ± 2.6 second^{-1} for the patients unpurified hemolysates and 41.8 ± 2.7 second^{-1} for the normals. In order to investigate whether or not these kinetic alterations were a result of the hemoglobin mixture itself or the associated molecular environment (organic phosphates, etc.) we subjected the four normal hemolysates and two patient hemolysates to G-100 Sephadex* chromatography in 0.1M NaCL and all samples were dialyzed overnight against deionized water at 4° C. This procedure was found to remove any detectable amount of 2,3-DPG and ATP. The results for the two patients purified hemolysates compared to the normal are presented in Fig. 3. The difference in kinetics observed in the unpurified hemolysates persisted even after purification. When 2,3-DPG was added to the hemoglobins they all responded by increasing the rate constant for deoxygenation. However at each incremental step the difference in kinetics persisted. These results, though empiric, seem to suggest that the difference between the two types of hemolysates lies in the hemoglobin itself. These differences in the purified hemolysates may be due to either an amino acid substitution in the main hemoglobin component (Hb A) or more probably an altered distribution of minor hemoglobin components known to exist normally in the red blood cells. We are presently investigating the latter possibility. Also being investigated is the rate of deoxygenation from whole blood in order to obtain deoxygenation constants which will be of more physiologic relevance.

The use of coronary arteriovenous oxygen differences to assay myocardial oxygen extractions is an unsatisfactory technique due to the heterogenous nature of coronary flow.[48,49] Coronary sinus blood represents a mixed venous effluent from virtually all

*It should be noted that in the paper from which this data was taken, it is stated that the hemoglobins were chromatographed on DEAE Sephadex. This was an error which was overlooked by the authors. The correct preparatory procedure is as stated herein.

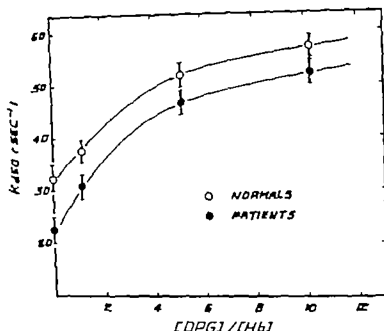


Fig. 3 The kinetics of oxygen dissociation from purified hemolysates of four normal individuals and ten patients in the absence of organic phosphates and in the presence of increasing 2,3-DPG concentration, plotted as the pseudo-first order rate constant for oxygen release (k_{dis}), calculated between 45 and 40 per cent saturation, versus the ratio of free 2,3-DPG to hemoglobin tetramer (Hb = 0.05 mM) (From Eliot, R. S., Salhany, J. M., and Mizukami, H. Angina and infarction occurring with patent coronary arteries and decreased rate of oxygen release. First Conference on Cardiovascular Disease Aspen, Colorado, 1970, Advances Cardiol. vol. 5, Basel, 1970, S. Karger AG.)

areas and layers of the left ventricle irrespective of regional variations in oxygen demand. In the absence of a precisely delineated ischemic process in the anterolateral wall of the left ventricle, even regional sampling within the great cardiac vein will be unrepresentative of local oxygen transport. There is a gradient in perfusion across the left ventricular wall from subepicardium to subendocardium[49,50] that may be in response to increased metabolic requirements of the latter.[50] Such localized areas of ischemia may well be biochemically masked in the venous drainage from the total region.

Discussion

The complexities of myocardial oxygenation are such that it is probable that multiple factors are responsible for cardiac cellular death. Numerous postmortem studies of myocardial infarction reveal a startling absence of recent vascular occlusion.[51-54] A lack of necrotic foci in the presence of vascular occlusion is frequently seen in atherosclerotic disease.[44] The acute vascular obstruction of thrombotic thrombocytopenic purpura may likewise be unattended by cardiac necrosis.[47] This condition results in extensive occlusive small artery disease of the myocardium. Of significance is the almost total absence of associated infarction. Obviously factors yet to be elicited are responsible for these apparent discrepancies.

It is in this light that we view disorders of oxygen transport. It is not reasonable to attribute myocardial infarction solely to this dysfunction. Indeed, the number of patients with myocardial infarction who exhibit no other known abnormalities comprises only a small fraction of the population. It is unlikely that they possess a monopoly on abnormal oxygen transport. It is most probable that disorders of oxygen transport represent a contributory factor in the pathophysiologic continuum of ischemic heart disease.

Tissue oxygenation is predicated upon delivery of adequately oxygenated blood to

the areas of need and coronary artery disease may preclude or limit this. The rheologic influences of increased blood viscosity and hyperlipidemia[47,48] may be compounded by an additional adverse effect on plasma-oxygen transport. The coating of erythrocyte membranes in a lipid rich plasma may conceivably interfere with the transfer of oxygen to the exterior of the cell at present this remains speculative

The myocardium itself represents a physiologic oxygen sink extracting more oxygen per weight and unit time from its blood than any other organ[1] It has been suggested that blood gases (CO_2 and O_2) do not come to complete equilibrium during passage through tissue capillaries[50] If equilibrium is not attained then the mechanism of oxygen delivery to tissue would be better assessed by measuring the actual rate of oxygen release from blood rather than by constructing an oxygen equilibrium curve

The final common pathway of ischemic myocardial necrosis has yet to be elucidated A reasonable probability is the activation of lysosomal enzyme systems through the dysfunction of oxygen-dependent pathways Chance has shown the half oxidation point ($I\ O_2$) of the terminal cytochrome (a_3) to be less than 0 1 mm Hg[51] and thus electron transport may continue at extremely low levels of oxygen tension However coronary sinus Po_2 values of 19 to 25 mm Hg have been recorded during peak anginal pain[8] these values are of course those of a mixed venous effluent from the coronary bed as discussed above True tissue levels in selected areas may be well below coronary sinus $I\ O_2$ Indeed a 15 to 20 mm Hg decrease in Po_2 has been shown from the subepicardium to the subendocardium[16] this is in accord with the demonstrated ischemic vulnerability of the latter region[52] Yet it is unlikely that less than profound alterations in oxygen transport would alone be sufficient to deter cytochrome function However the hepatic hydroxylase system is sensitive to changes in Po_2 in the order of tens of millimeters of mercury[53] This is in the range of changes wrought by 2 3-DPG and other affectors of the hemoglobin-oxygen interaction providing a non cardiac model of enzyme vulnerability to dysfunction of the oxygen transport mechanism

Similarly significant alterations in the rate of release of oxygen from hemoglobin may well be critical to tissue oxygenation and may represent a partial explanation for myocardial hypoxia in the presence or absence of a compromised vasculature. This hypothesis remains to be rigorously tested but currently provides an intriguing association between dysfunction of the hemoglobin-oxygen interaction and myocardial oxygenation

In the race for tissue oxygenation those individuals with a decreased rate of oxygen release start with a handicap that may or may not be compensable. Their ability to compete will largely depend upon the existence of additional handicaps within this system and the integrity of available compensatory mechanisms.

Summary

The occurrence of myocardial infarction in the presence of patent coronary arteries and the poor correlation between acute vascular occlusion and myocardial infarction indicates that ischemic heart disease is a multifactorial entity The release of oxygen from hemoglobin is the basic step in tissue oxygenation and this function has traditionally been assayed by equilibrium measurements. A more physiologic approach may be the determination of the rate at which oxygen is actually released from whole blood The speed of this reaction is directly proportional to erythrocytic levels of 2 3 DPG ATP and acidity

Clinically kinetic alterations of the hemoglobin-oxygen interaction are seen in sickle cell anemia carbon monoxide intoxication and to date in a small group of patients with ischemic heart disease and normal coronary arteriograms The importance of abnormal oxygen transport in ischemic heart disease remains to be determined Its role may well be that of a contributory factor in the pathophysiologic continuum of myocardial ischemia and infarction and its study provides a new approach to problems of tissue oxygenation

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Appraisal and reappraisal of cardiac therapy

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The clinical use of serum cardiac glycoside concentration measurements

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After nearly 200 years of clinical experience in the use of digitalis glycosides, the narrow margin between the therapeutic and toxic effects of this class of drugs continues to present problems to the clinician. In a recent series of 931 consecutive admissions to a medical service, 15 per cent were on maintenance digitalis therapy and of these 135 patients, 23 per cent were considered to have definite electrocardiographic (ECG) evidence of digitalis toxicity. An additional 11 per cent were grossly under-digitalized. The in-hospital mortality rate of 41 per cent among definitely toxic patients, although by no means solely due to digitalis toxicity, serves to further emphasize the gravity of the clinical setting in which digitalis poisoning is frequently encountered.

Recent advances in techniques for measurement of cardiac glycoside concentrations in serum or in plasma[1] now promise to make such information more widely available to the physician faced with a clinical problem related to the use of these drugs. Our own experience with more than 6,000 measurements of serum digoxin and digitoxin levels in a broad spectrum of clinical circumstances is based on a radio-immunoassay approach. Modifications of our original method have improved both the speed and convenience with which results can be obtained.

In the case of digoxin (Fig. 1), serum samples as small as 0.1 ml. can now be readily measured using phosphate-buffered saline to bring the system to a convenient volume. Following the addition of tritiated digoxin tracer and a suitable amount of digoxin-specific antibody, a short incubation allows an equilibrium to be reached in which tritiated digoxin tracer competes with unlabeled digoxin in the sample for a limited number of antibody combining sites. Dextran-coated charcoal is then added, resulting in selective adsorption of free tritiated digoxin, which is separated by centrifugation. Antibody bound tritiated digoxin remaining in the supernatant phase is decanted into a toluene-detergent base scintillation counting fluid and counted in a liquid scintillation counter using a ^{133}Ba external standard for quenching correction. A typical standard curve relating per cent of antibody bound tracer counts to a logarithmic plot of unlabeled digoxin in the sample is shown in Fig. 2A. A sensitivity of 0.2 ng. per milliliter is apparent, with good resolution over the concentration range of clinical interest.

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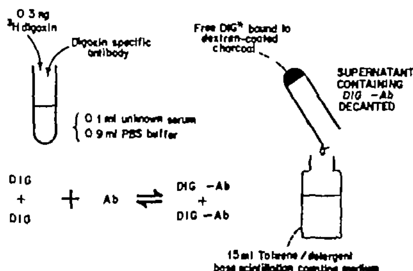


Fig. 1. General scheme of serum digoxin radioimmunoassay. *DIG*, digoxin. *DIG**, ³H-digoxin. *Ab*, digoxin specific antibody. (See text for details.)

In order to facilitate computer usage we now use the type of standard curve plot shown in Fig. 2B. Known concentrations of unlabeled digoxin plotted on the horizontal axis bear a linear relationship to reciprocal antibody bound tracer counts. A computer program corrects all sample counts for background and quenching plots the standard curve (run with each set of unknowns) by least squares linear regression analysis, and prints out values for unknown samples. Minor modifications allow reliable estimates for single samples to be obtained in about one half hour with little sacrifice in precision and one technician can run fifty samples in duplicate in a normal working day without difficulty.

The commercial availability of a digoxin analogue with a radioactive iodine label suitable for use as a tracer in the system will further extend the availability of the digoxin radio-immunoassay method to the laboratory or hospital with gamma counting equipment but lacking a liquid scintillation counter.

As suggested by Doherty, Perkins, and Flanigan[3] on the basis of a relatively constant ratio between serum and myocardial digoxin concentrations at equilibrium the serum digoxin concentration has been found to bear a meaningful relationship to the clinical effect in a number of circumstances. Experience with radio-immunoassay methods, as well as other approaches to glycoside concentration measurements,[2] has shown that highly significant differences in mean serum or plasma levels exist between groups of patients with and without evidence of digoxin toxicity.[4] Similar observations have been made in the case of digitoxin and also digitalis leaf measured as digitoxin. Our initial experience with hospitalized patients on stable maintenance digoxin doses has shown that 131 nontoxic patients had a mean serum digoxin concentration of 1.4 ng. per milliliter (±0.7 S.D.) while a group of 48 patients with ECG evidence of digoxin toxicity had a mean level of 3.7 ± 1.0 (P < 0.001).[4] Ninety per cent of patients without evidence of toxicity had serum levels of 2.0 ng. per milliliter or below whereas levels above 2.0 ng. per milliliter were observed in 87 per cent of patients with digoxin intoxication which disappeared when the drug was withheld. Another series of patients studied at St. Bartholomew's Hospital and the National Heart Hospital London by Chamberlain and associates[6] yielded similar results. The mean serum digoxin concentration was 1.4 ng. per milliliter (± S.D. 0.7) among 116 patients without toxicity while among those with overt cardiac toxicity the mean was significantly higher at 3.1 ± 1.1 ng. per milliliter (P < 0.001). Twenty-one of the 22 digoxin toxic patients had serum concentrations ranging from 2.0 to 5.2 ng. per milliliter. As is apparent in both of these series, overlapping values were noted in a small but certainly not negligible group of patients, and the degree of overlap observed in another group

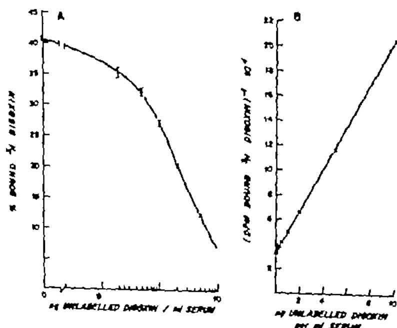


Fig. 2. A, data from the experimental procedure outlined in Fig. 1 and in the text. This standard curve plots per cent antibody bound ³H-digoxin against the logarithm of unlabeled digoxin concentration in the sample. Horizontal lines delimit ranges of duplicate determinations. B, The same data plotted as the reciprocal antibody bound counts against unlabeled digoxin concentration. The rectilinear plot obtained is consequence of restricted heterogeneity of antibody binding site affinities.

of patients prospectively evaluated at the time of admission to the hospital was somewhat greater still.

The assessment of the individual patient thus requires an integrated approach in which serum glycoside concentration data are evaluated in the clinical context with due recognition of the multiple factors which may influence myocardial sensitivity to digitalis. Among the best documented of these are serum potassium, sodium, calcium, and magnesium concentrations, hypoxia, acid base balance, autonomic tone, thyroid status, and concomitant treatment with other cardio-active drugs. The nature and severity of intrinsic cardiac disease are undoubtedly important determinants as well, as dramatically reflected in the disparate effects of massive suicidal or accidental doses of digoxin in patients with and without pre-existing heart disease.

Qualitatively similar conclusions have been reached in a study of the correlation between serum digoxin concentration and acetyl strophanthidin tolerance in hospitalized patients with cardiac disease.[8] A highly significant inverse correlation was observed between serum digoxin concentration and acetyl strophanthidin tolerance in 45 patients receiving digoxin. Nevertheless, variation in acetyl strophanthidin sensitivity was demonstrated among individual patients with similar serum digoxin concentrations. A parallel experimental study in collaboration with Drs. Barr, Klein, and Lown[9] has shown that in the dog changes in acetyl strophanthidin tolerance induced by digoxin were inversely related to serum digoxin concentration over a range from 0 to 15 ng per milliliter. In addition, digoxin-induced changes in ventricular automaticity as assessed by repetitive ventricular responses to low energy endocardial stimuli were also related to serum digoxin concentration.

In the case of digitoxin, both Na+—K+ ATPase inhibition assay[10] and radioimmunoassay[11] have provided evidence of significantly higher mean serum concentrations in patients with evidence of toxicity compared with nontoxic control subjects. Once again an intermediate range of

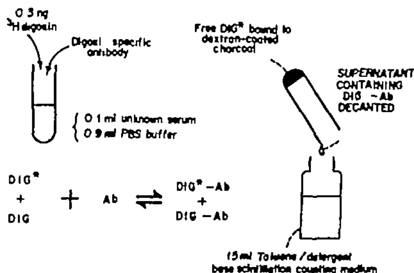


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a given patient may or may not manifest signs or symptoms of toxicity depending upon the same clinically important variables mentioned above.

In addition to supplying data useful in the management of individual problem patients, current methods for measurement of serum cardiac glycoside concentrations also have relevance to the investigation of other aspects of the clinical pharmacology of the digitalis glycosides. Using methods analogous to those previously described for digoxin and digitoxin, we have recently developed a radio-immunoassay for plasma and urinary ouabain concentration with a sensitivity of less than 0.1 ng. per milliliter.[12] Using this method, it has been possible to determine a mean plasma ouabain half life of 21 hours in normal human subjects, a value in good agreement with the 22 hour half time of pharmacologic effect observed by Weissler and co-workers[13] using systolic time intervals.

Other areas in which radio-immunoassay methods have facilitated studies of the clinical pharmacology of digitalis glycosides include observations of the absorption of orally administered digoxin from the gastrointestinal tract. Following ingestion of 0.5 mg. of digoxin in tablet form, peak plasma levels were reached in healthy fasting subjects at about one hour, followed by a fall to the final excretory plateau by about 6 hours.[14] The same dose following a meal resulted in a significantly lower peak plasma concentration but no significant difference remained at the end of two hours or thereafter. These data serve as a reminder that blood samples for digoxin assay should not be drawn earlier than 5 to 6 hours following an oral dose, since valid interpretation requires that full drug distribution equilibrium be attained between serum or plasma and myocardium.[15]

In contrast to the relative constancy of the digoxin absorption pattern in normal subjects, patients with malabsorption syndromes have been found to absorb the drug poorly and erratically.[16] Malabsorption of digoxin was particularly marked in patients deficient in intact small bowel mucosa (as in sprue or short bowel syndrome) or in whom rapid transit time compromised mucosal contact. Digoxin absorption appeared to be relatively normal in two patients with pancreatic insufficiency.

Another investigative area of practical interest has been the effect of cardiopulmonary bypass on plasma digoxin concentration and total body digoxin stores. Studies employing radio-immunoassay techniques have shown that despite a transient fall in digoxin concentration during bypass due to dilution of plasma volume by pump prime and transfusion, mean serum or plasma concentration returned to preoperative levels or somewhat above during the initial postoperative day.[17, 18] Measurement of urinary digoxin loss and loss into pump and discard sucker bottle demonstrated a mean loss of only 0.14 mg. during the procedure, almost all of which was via renal clearance.[17]

Radio-immunoassay has also been used to explore the relationship between the plasma digoxin concentration and the ventricular response to atrial fibrillation in patients on chronic oral maintenance doses of the drug.[4] Among patients with intact atrioventricular conduction systems who had demonstrated the ability to respond with ventricular rates of greater than 120 beats per minute during the year prior to the study, an inverse relationship between ventricular response and plasma digoxin concentration was shown. As might be expected, resting heart rate did not correlate well with plasma digoxin concentration among patients with intrinsic disease of the conduction system.

Human fetal and neonatal digoxin studies represent a final example of the utility of radio-immunoassay methods in studying special aspects of the clinical pharmacology of digitalis glycosides.[19] Pregnant women with rheumatic heart disease on maintenance digoxin doses were found to have serum digoxin concentrations at term which were the same as the concentrations in cord blood from the fetus at the time of delivery, documenting the transplacental passage of the drug. Also of interest was a significant rise in mean serum digoxin concentration of the mothers during the first postpartum month without change in the maintenance digoxin dose, apparently due to the expected postpartum fall in the glomerular filtration rate and hence in the rate of digoxin excretion.

The available evidence, then, seems to support the concept that serum or plasma concentrations of digitalis glycosides bear a significant relationship to cardiac effects. Knowledge of these concentrations can now be gained by the application of relatively simple, rapid and precise assay procedures. Such methods are clearly of use in studies of the clinical pharmacology of cardiac glycosides. The ultimate role of serum or plasma digitalis assays in the management of individual problem patients, however is more difficult to define. Observations in the clinically difficult group of patients with equivocal ECG signs of digoxin excess suggest that serum levels are quite likely to fall in the "gray area" around 2.0 ng per milliliter but with scatter above and below this level.[1] In addition, serum digoxin concentrations substantially above 2 ng per milliliter are sometimes required to adequately control ventricular response to atrial fibrillation or flutter. Thus one is still faced at times with the necessity to follow *Withering's advice*: "Let the medicine therefore be continued until it either acts on the kidneys, the stomach, the pulse, or the bowels; let it be stopped upon the first appearance of any one of these effects . . . ."[20] The availability of more rapidly acting digitalis preparations and sophisticated monitoring techniques now allow such observations to be made at minimum risk to the patient.

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Annotations

Valsalva maneuver made easy

In diagnosing idiopathic hypertrophic subaortic stenosis, it is often useful to have the patient perform a Valsalva maneuver.[1,2] Many patients however have difficulty comprehending instructions on how to perform the maneuver or in actually executing it.

We have found that this difficulty may be overcome by having the examiner place his clenched fist against the patient's epigastrium and having the patient push against the fist with his abdomen. In the process of doing this, a Valsalva maneuver (straining against a closed glottis) is unconsciously performed and the desired objective is achieved.

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Kidney transplantation

So much has been written about organ transplantation from so many different points of view that the results and potential of therapeutic kidney grafting may have been obscured. This procedure is now well established and combined with a sensible dialysis policy it should be possible to offer treatment to all those in need at an economical cost; yet, due to a variety of nonmedical difficulties, only a small fraction—about 10 per cent—of young people in terminal renal failure are receiving care. Since the introduction of effective immunosuppressive drugs, azathioprine and steroids, in 1961 there has been a steady improvement in the results of renal transplantation. According to the Kidney Transplant Registry the percentage of functioning grafts after two years from cadaver donors up to 1965 was less than 20 per cent but by 1969 the figure was 40 per cent. In a combined series from Cambridge, Hammersmith and Edinburgh, the two-year graft survival from cadaver donors is 56 per cent. The patient survival is considerably better due to the availability of dialysis. For close related living donors, an 80 per cent two-year graft survival can be achieved.

In theory, with cadaver renal transplantation using only excellent donor-recipient tissue matched organs, it should be possible with conventional immunosuppression to approach the results of close blood relative donors. Further improvements might be expected with better immunosuppression, for example anti-lymphocyte globulin. These objectives can only be reached if there is a large pool of tissue-typed recipients, close collaboration between transplantation centers, and an adequate supply of donor kidneys. Lack of donor kidneys is the main stumbling block. This is not because too few people die with suitable kidneys—unfortunately road accidents, cerebral hemorrhage and cerebral tumors could provide more than enough kidneys—but most of these organs are not being used due mainly to lack of positive cooperation within the medical profession. The main ethical dilemma in renal transplantation is the failure to treat most young patients in renal failure. If correct results and potential improvements were more widely appreciated by medical men and the public, then charitable donation of organs would be the expected procedure i

suitable cases and all those in need of kidney graft would be offered treatment.

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Fat cells nutrition and obesity

As Knittle and associates have shown for rats and man, the number of fat cells in the body is determined by the state of nutrition during the early periods of postnatal life. When the subject is well fed or overly fed immediately after birth and before cell proliferation or growth ceases, the number of fat cells increases and may even exceed three times the number in animals that are calorically undernourished or not overly fed. Once growth and cell proliferation cease, the number of fat cells is constant throughout the remainder of life. Furthermore, once cell number becomes fixed, the quantity of fat stored is reflected in the quantity stuffed into each fat cell, regardless of the number of cells. Thus, fat man with three times the number of fat cells can store three times as much fat in his body all else being equal, as man who, in early life, was not overly fed and who, in turn, has one third the number of fat cells. Therefore the time to prepare to prevent obesity is at birth and during the period of maturation. Once the number of cells in the body is established, variations in caloric intake can vary only the amount of fat stored within the cells and not their number. Furthermore, person with three times the number of fat cells must diet fairly rigidly to reduce the quantity of fat in each cell to one third of its full capacity. He still would be as "fat" as the man with one third the number of fat cells who eats excessively and has his fat cells fully stuffed. The fat man with three times as many fat cells fully stuffed with fat would be essentially three times as big as the fat man with one third as many fat cells fully stuffed. Thus, control of obesity would be difficult and dieting would have to be more rigid for the person with three times the number of fat cells. To be skinny this person many fat cells would have to contain lower percentage of fat per cell than those of the man with one third the number of fat cells.

Therefore, according to the findings of Knittle and associates, nutrition during the prematuration period of life and the number of fat cells in the body probably explain in large part why some fat people have difficulty in losing fat and in reducing their weight.

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Familial nephropathy

Familial nephritis has been recognized and described under various names since 1875 but it was Alport[1] in 1927 who observed the associated bilateral nerve deafness and clearly defined the syndrome. Other investigators have described the ocular manifestations of this entity. Despite the fact that over 65 affected kindred have been reported on, the disease is poorly understood and probably underdiagnosed.

The clinical and laboratory manifestations have been summarized by Perkoff and Royer.[2,3] These include variable hematuria, proteinuria, and occasional pyuria at the onset of the disease. Renal function is usually normal in the initial phase and about 50 per cent of the patients have or develop bilateral nerve deafness, this being slightly more common in boys than in girls. Males are said to develop renal insufficiency after the age of 20 and

Table I. Summary of major renal histologic findings

Patient	Age at biopsy	Sex	Glomerular		
			Hyalinization	Glomerular basement membrane thickening	Centrolobular proliferation
1	14	M	0	++	++
	19½		0	+++	+++
2	9½	M	0	++	0
	15		0	++	++
3	8	M	+	0	0
	14½		0	0	++++
4	8½	M	0	0	+
	10½		0	+++	+++
5	6	F	0	0	0
	11		0	++	+
6	11½	M	0	++	++
	12		0	+++	+++
	13		0	+++	+++
7†	9 nephrectomy	F	++++	0	+++
8	7	F	0	++	++
	10½		+	0	+
9	17	F	+	0	0
10	13	F	0	++	0
	14½		0	0	0
11	12½	F	0	+	0
12	16	M	+	++	0
	18		+	0	0
13	18	F	0	+++	0
14†	12	F	0	+++	++
	12½		++++	++++	+++
	13		++++	++++	++++
15	12 autopsy	F	++++	+++	++++
16	5	M	0	+	+
	8		+	0	+
17	8½	M	0	++	++
	11			No glomeruli	
18	4	M	0	+++	++
19	6	M	+	++	+++
20	8½	M	0	++	++
21	6½	M	0	++	0
	10		0	++	0
22	15	M	0	+	+
	19		0	0	0
23	17	M	0	+	+
	21		0	0	0

Patients 1 through 14 are siblings; 15 and 16 are siblings; 17 and 18 are siblings; 19 to 21 are siblings; 22 and 23 are siblings.
Grade 0 = Normal; + = minimal; ++ = mild; +++ = moderate; ++++ = severe.
*Decreased renal function.
†Renal failure; Patients 7 and 14 have received transplants.

die before 40, while the affected females live a relatively normal life.

The natural history of the disease and the morphologic changes are very poorly understood because most patients have been studied either in the early stages or very late stages of their disease. In addition, no immunohistologic evaluation has been done. We therefore undertook a serial morphologic evaluation of this entity.

Twenty-four patients from 17 families were studied. Specimens of renal tissue were obtained from 23 of these patients and studied by light and immunofluorescent microscopy. Serial biopsies were obtained from 15 of these patients. The patients

Epithelial proliferation	Tubular atrophy	Interstitium				Blood vessels
		Inflammation			Foam cells	
		Fibrosis	Acute	Chronic		
0	0	0	0	0	0	0
++	0	++	0	+	0	0
0	0	0	0	0	0	0
0	+	++	0	+	0	0
0	0	+	0	+	0	+
++	+	++	0	++	0	0
0	++	++	0	0	0	0
+	++	+++	0	+	++	0
0	+	0	0	0	0	0
0	+	++	0	0	0	0
++	++	++	0	+	0	+
++	++	+++	0	++	0	+
+++	+++	++++	0	+++	+	++
++++	++++	++++	++++	++++	0	+++
0	++	+	0	0	0	0
0	0	+	0	0	0	0
0	++	+	0	0	0	0
0	++	++	0	+	0	0
0	0	0	0	0	0	0
0	0	++	0	0	0	0
0	+	+	0	0	0	0
++	++	++	0	++	0	0
0	0	0	0	0	0	0
0	+++	+++	++++	++++	++	0
++++	+++	+++	++++	++++	++	+++
++++	+++	++++	++++	++++	++++	++++
++++	++++	++++	0	++++	++++	++++
0	++	+	0	+	++	0
0	0	0	0	+	0	0
0	++	+	0	+	0	0
	0	0	0	0	0	0
0	0	+	0	0	0	0
+++	0	++	0	0	0	+
+	0	++	0	0	0	0
0	0	+	+	0	0	0
0	0	+	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0

were followed from 1 to 11 years, ranged in age from 7 t 21 years and had opthalmologic, audiologic, and renal f nction tests performed periodically.

Hematuria was present in all patients and was usually the presenting complaint. Proteinuria was present in 71 per cent and hearing loss in 42 per cent. Three female subjects developed severe renal failure.

The details of the clinical and pathologic studies are presented elsewhere. There was no correlation between morphology renal function, and urinary sediment except in patients with renal failure. The morphologic picture was one of slow progression

in most instances with a mixed glomerular and interstitial nephritis. Glomerular basement membrane thickening was the earliest and most common lesion seen while the most marked changes were in the interstitium with progressive interstitial fibrosis a prominent feature in subsequent biopsies. The severity of the lesions tended to increase with age. The lack of interstitial foam cell in most patients was notable. To date, most of our male patients have shown no deterioration in their renal function and in several there has been no progression in the morphologic abnormalities despite the presence of known disease for at least 11 years in one family.

A definite pattern is evident when serial renal biopsies are studied. The lesions initially are usually mild and progress slowly. Early, there are commonly only *glomerular basement membrane changes* occasionally with some elements of interstitial nephritis. These changes are frequently said to be nonspecific or nondiagnostic. As the disease progresses with age the interstitial lesions predominate often with some progress in the glomerular lesions. The immunofluorescence (IgG, β C, fibrinogen) is negative in all patients. This combined picture should suggest the diagnosis even without the clinical history.

In our experience in addition to recurrent benign hematuria, focal glomerulonephritis, and healing post-streptococcal nephritis, a significant number of patients with hematuria had familial nephritis. Therefore it may be important to do serial audiologic and ophthalmologic examinations on any child with hematuria. Furthermore the prognosis in affected males is not uniformly poor nor are the females to be generally considered free of the risk of serious disease.

We suggest as one possible pathogenetic mechanism a metabolic or enzymatic defect in the biosynthesis or metabolism of collagen. This speculation is based on the early appearance of basement membrane lesions and certain clinical and immunologic similarities between the glomerular basement membrane and the lens capsule collagen.

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Healed bacterial endocarditis

To the Editor:

The paper "Mitral stenosis and insufficiency: A complication of healed bacterial endocarditis" by Dr Bentsch (Am. Heart J 82:39 1971) is an article in which I cannot find any clinical or pathological proof that the cases presented by the author are indeed caused by healed bacterial endocarditis.

I do not doubt that *healed bacterial endocarditis* could indeed cause mitral insufficiency but the "proof" supplied by the author certainly is not convincing. The report consists of three cases of mitral stenosis in which calcified vegetations were found and mitral insufficiency was present in each case. I think the author as any practicing clinician or pathologist, should be aware that sterile vegetations are possible. They are, as a matter of fact, quite common. To prove this point is very easy

(laboratory animal, such as dog, if anyone injures the mitral valve (cuts into leaflet or cuts portion out of the leaflet I myself conducted large series of similar experiments many years ago), the result will be mitral regurgitation and sterile vegetation on the valve, which usually calcifies. I therefore contend that (1) the cases presented do not bear the necessary proof, nd (2) that calcified vegetations are not proof of previous bacterial endocarditis.

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Reply

To the Editor

Dr Robicsek production of mitral regurgitation and sterile vegetations in animals with injured valves is of interest but does not pertain to the cases in question. The report stressed the development of mitral stenosis from large calcified vegetations which obstructed the valve orifice. This inevitably produced insufficiency of the valve, a well-known consequence of healed bacterial endocarditis. That the vegetations were bacterial in origin is impossible to prove with total certainty however the presence of underlying valvular ulceration nd deformity the large size of the vegetations, their complete calcification, and the presence of an associated healed rheumatic valvulitis conform to all previous diagnostic criteria,[2,3] and make any other explanation extremely unlikely

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Manufacturers of permanent pacemakers

To the Editor:

It is often of great importance to know the manufacturer of permanent pacemaker

Walter and Wenger[1] have pointed out the characteristic radiographic shadow typical for each of the major brands of pacemakers manufactured in the United States. Frequently the arrangement of cells in the battery pack allows specific identification of the model number

Unfortunately some x-ray films are not of high enough quality to distinguish the various shapes accurately Furthermore the paper by Walter and Wenger may not be always readily vailable.

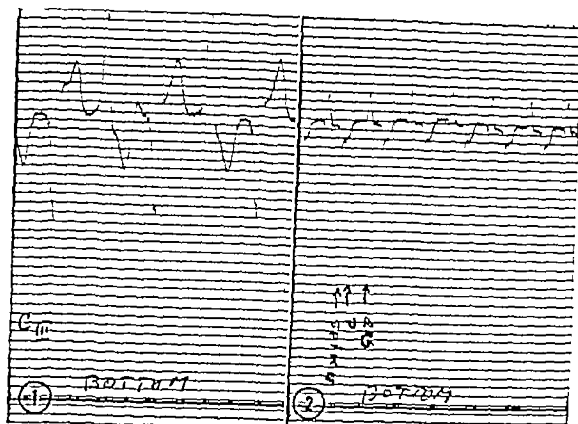
It seems to me that each manufacturer could easily indicate the brand name and model number in radiopaque lettering as part of each permanent pacemaker power pack. Thus the chest x-ray film would not only show the position of the electrode within the heart, nd the outline of the battery pack, but would also indicate Ectocor "Medtronic, Medtronic-585 or whatever

I do not believe that there are any technical reasons why this could not be done and it might save great deal of trouble and time in emergency situations.

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Bidirectional tachycardia

To the Editor

In the clinical communication "The mechanism of bidirectional tachycardia" by Rosenbaum, Elizari and Lazzari (AM. HEART J. 78:4, 1969) the authors advanced an interesting mechanism to explain most, if not all, bidirectional tachycardias (BT).

We recently had the opportunity to study a case of BT in a 35-year-old Caucasian woman who first became ill some two and a half months before being admitted to our hospital. Her disease began with a short episode of fever and malaise which was soon followed by features of congestive heart failure. After one month of treatment including digitalis, she noticed palpitations. After admission to the hospital she presented a picture of almost permanent BT (Fig. 1) which persisted at a ventricular rate of 136 beats per minute in spite of the discontinuation of digitalis.

Because we had in mind the communication of Dr. Rosenbaum and associates but could not, as in the original study, clearly distinguish the P waves in the ECG, we were led to challenge the author's hypothesis by artificially pacing the patient's right atrium.

Surprisingly we observed the disappearance of the BT and the appearance of a normal QRS duration, although the paced rate at 166 beats per minute was superior to the spontaneous rhythm (Fig. 2). This observation certainly does not fit the authors' hypothesis of "alternant aberrant conduction in the divisions of the left bundle branch." In the case under our observation, it became certain that the tachycardia was ventricular in origin.

We suggest that this kind of artificial atrial pacing should be used to demonstrate the supraventricular origin of BT whenever there is some uncertainty about the P waves.

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Reply

To the Editor

The ECG reported by Drs. Ghita Mihai and Kleinerman Lazar looks like bidirectional tachycardia (BT). However, it differs significantly from all the cases reported by us[1] or reviewed from the literature. Differences are as follows:

(1) The ventricular rate is much slower in the present case (136 beats per minute, while in our cases it ranged between 142 and 214 beats per minute).

(2) In the cases reported by us, Lead V1 showed a right bundle branch block (RBBB) configuration in both alternant patterns, and the same configuration was found in all other cases reviewed from the literature, whenever Lead V1 was available. Conversely, in the present case, one of the QRS complexes (the one beginning the strip V2/V1/V5) is the peculiar left bundle branch block (LBBB) pattern that we have described[2,3] as arising close to the main papillary muscle of the right ventricle. This configuration can never occur during aberration of supraventricular beats and is in itself indicative of a ven-

tricular origin. This pattern probably corresponds to the pattern with right axis deviation in the limb leads. The other QRS configuration is one of RBBB with left axis deviation, indicating focus of origin somewhere in the posterior wall of the left ventricle.

(3) In our cases, the alternant beats were evenly spaced, whereas in the present case, the LBBB pattern occurs 0.04 to 0.06 second earlier than the RBBB pattern. Accordingly it is quite obvious that the mechanism of the present case must be different from the one we have postulated for most cases of BT

Two possibilities may be considered.

(1) The case reported may be idioventricular tachycardia (rate, 68 beats per minute) of the RBBB pattern, plus ventricular extrasystoles of the LBBB pattern which are bigeminated and interpolated. This would require entrance block" in the idioventricular focus, which could then be thought of as parasystolic rhythm.

(2) A much more likely possibility is ventricular tachycardia (rate, 136 beats per minute) of the focus eliciting the RBBB pattern, plus ventricular bigeminy of the focus eliciting the LBBB pattern. Half the beats of the ventricular tachycardia would be eliminated (and replaced) by the extrasystolic beats, simply because of interference. The coupling of the extrasystoles is close to the diastolic length of the ventricular tachycardia (only 0.04 to 0.06 second less actually this is practically the maximal possible coupling under this particular set of circumstances) If such is the case, and if the extrasystolic beats discharge the focus of ventricular tachycardia, the temporal relationship between the two ectopic foci would remain the same throughout namely the difference between the two diastolic intervals will always be of only 0.04 to 0.06 second duration. It should be noted that, if the ventricular focus is "protected, the difference between the two diastolic intervals would be doubled, and the appearance of simple ventricular bigeminy would become so clear that the aspect suggesting BT would be lost. Whatever the mechanism, it is our feeling that in the present case we are dealing with a form of bigeminy no matter how close the two different diastolic intervals are to an even spacing. On the other hand, an even spacing is theoretically and practically an essential requisite in true BT

The question arises whether this manifestation should still be called BT Perhaps it should, because morphologically" it looks like it. Then, it should be accepted as another" mechanism of BT However if our interpretation is correct, it is obvious that, with the same mechanism, tracing may occur without bidirectional aspect. Perhaps each situation should simply be identified by the corresponding mechanism.

Drs. Ghita and Kleinerman should be congratulated for their extremely original and simple idea of testing the mechanism of BT by pacing the atria t rates faster than the prevailing mechanism, whenever possible. This may certainly throw further light on the mechanism of this arrhythmia. However it should be stressed that, even without resorting to atrial pacing the different mechanism of the present case was clearly apparent.

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Book reviews

BRITISH MEDICAL BULLETIN. *Management of Renal Failure.* Vol 27, No. 2. Edited by M. D. Milne. London, May, 1971. The Medical Department. The *British Council.* 190 pp.

The British Medical Bulletin has established a tradition of excellent publications and the present volume is no exception. D. A. K. Black has gathered eminent authors with excellent articles on the management of renal failure. The papers include medical and surgical management of acute renal failure, medical care of the uremic, peritoneal dialysis and hemodialysis, home dialysis, dietary management and transplantation. Every doctor in general practice, internal medicine and renal surgery will find this issue worth owning.

CEREBRAL VASCULAR DISEASES. Seventh Conference. James F. Toole, Chairman. Edited by John Moossy and Richard Janeway. New York, 1971, Grune & Stratton, Inc. 258 pp. Price $9.75.

These transactions of the Seventh Conference on Cerebral Vascular Diseases summarize the symposia held in Princeton, N. J., from Jan. 7 to 9, 1970. The subjects discussed included spinal cord vascular diseases, cerebral edema and cerebral vascular diseases, techniques for diagnosis of obstructive vascular diseases, cerebral blood flow and metabolism, acceleration, weightlessness, and the cerebral circulation, cerebral vascular insufficiency, and intracranial arterial aneurysms. Numerous participants briefly review these many problems in short articles accompanied by clear diagrams and illustrations. As usual in symposia the discussions are interesting and informative. Those interested in the central venous system and in the vascular systems will find this book (as well as the first six transactions) worth owning.

HANDBUCH DER EXPERIMENTELLEN PHARMAKOLOGIE (HANDBOOK OF EXPERIMENTAL PHARMACOLOGY). Edited by O. Eichler, A. Farah, H. Herken, and A. D. Welch. Band XXVII. Antikoagulantien. Edited by F. Markwardt. New York, 1971, Springer-Verlag. 598 pp. Price $54.50.

This volume of the series of Handbooks of Experimental Pharmacology reviews quite thoroughly the problems of anticoagulants. The contributors include discussions of the physiology and biochemistry of the coagulation of the blood, methods of study, descriptions of the various anticoagulants, clinical and experimental applications, and various problems connected with and indications for the use of these agents. There are extensive bibliographies following each chapter and the volume contains a good index. The paper is light and not shiny. This is a good book to have even though it deals with a subject already well covered in the literature.

VENOUS THROMBOSIS AND PULMONARY EMBOLISM. By Michael Hume, M.D., Simon Sevitt, M.D., M.Sc., F.R.C.Path., F.R.C.P.I., and Duncan P. Thomas, M.D., B.Sc., D.Phil. Cambridge, Mass., 1970, Harvard University Press. 456 pp. Price $16.00.

This book brings together a considerable amount of information on an important clinical issue. In spite of much interest in and work with these two problems, venous thrombosis and pulmonary embolism remain common causes of illness and death, as well as being complications of many other disease states. Their incidence has not declined and the treatment has remained unchanged for many years. The authors, together with several contributors, review the incidence, pathology, predisposing factors, mechanisms and pathogenesis, clinical manifestations, diagnosis, and the medical and surgical treatment. Unfortunately, the discussions are not complete and only certain aspects of the problem are presented. The bibliography, as in most modern publications, is almost entirely composed of references to fairly recent material. Those who have been interested in this field know that little progress has been made and that most reports describe studies that are not really new. This field, like most areas in medicine, lacks new ideas. Nevertheless, those who wish to review the subject of thromboembolism will find this book on venous thrombosis and pulmonary embolism to be valuable and accurate.

Books received

DIAGNOSTIC APPROACHES TO PRESENTING SYNDROMES. Edited by Jeremiah A. Barondess, M.D. Baltimore, 1971, The Williams & Wilkins Company. 547 pp. Price $21.50.

PSYCHIATRIC ASPECTS OF ORGAN TRANSPLANTATION. Edited by Pietro Castelnuovo-Tedesco, M.D. New York, 1971, Grune & Stratton, Inc. 172 pp. Price $7.75.

CARDIOLOGY: A Clinicophysiologic Approach. Edited by Stephen M. Ayres, M.D., and John J. Gregory, M.D. New York, 1971, Appleton-Century-Crofts. 667 pp. Price $15.00.

Respiratory Function in Disease. Ed. 2, An Introduction to the Integrated Study of the Lung. By David V. Bates, M.D., F.R.C.P., Peter T. Macklem, B.A., M.D., C.M., F.R.C.P., and Ronald V. Christie, M.D., M.Sc., D.Sc., Hon.D.Sc., F.A.C.P., F.R.C.P. Philadelphia, 1971, W. B. Saunders Company. 584 pp.

A Primer of Haematology. By F. A. Ward, F.R.C.P.I., M.R.C.P.(Edin.). New York, 1971, Appleton-Century-Crofts. 106 pp. Price $6.50.

The Circulation: An Integrative Physiologic Study. By James P. Henry, M.D., and John P. Meehan, M.D. Chicago, 1971, Year Book Medical Publishers, Inc. 208 pp.

Announcements

Fundacion Viviana Luckhaus Prize

The Fundación Viviana Luckhaus has instituted the "International Prize Fundación Viviana Luckhaus, 1972." This prize is intended to honor a report of original research related to blood platelets (morphology, physiology, biochemistry, pathology, etc.) and/or their relationship to thrombosis and blood vessels, and to promote communication and interchange between research workers in different parts of the world.

For further information and rules for the 1972 contest, apply to Dr. Edgardo S. Sack, Fundación Viviana Luckhaus, Hospital Juan A. Fernández, Cerviño 3356, Buenos Aires, Argentina.

International Sessions of Cardiology

The "International Sessions of Cardiology," conducted annually in Paris, France, by Professors Facquet and Welti, will be held at the Department of Medicine, Pitié-Salpetrière, Monday through Wednesday, May 15 to 17, 1972. For complete information please contact Prof. Agrégé J. J. Welti, Hôpital Fernand Widal—200, Rue du Faubourg Saint Denis, Paris 10, France.

Postgraduate course in angiography

A postgraduate course entitled "Angiography: Advances in equipment and technical aspects" will be held January 26 through January 28, 1972, at the Sands Hotel, Las Vegas, Nevada. This course is sponsored by the Department of Radiology, Shadyside Hospital, in conjunction with the University of Pittsburgh School of Medicine. The course is intended for radiologists and cardiologists as well as other interested personnel involved in vascular examinations. Panel discussions by leading investigators will analyze existing equipment and future developments. Clinical presentations and personal opinions regarding all aspects of arteriography will be presented. For further information contact: The Secretary, Shadyside Hospital, Department of Radiology, 5230 Centre Ave., Pittsburgh, Pa. 15232.

Two NHLI programs invite research proposals

The Extramural Research and Training Program, National Heart and Lung Institute, invites applications for grants in support of specialized centers of research (SCORs) for research attacking high-priority problems in arteriosclerosis and pulmonary diseases.

The NHLI Lipid Metabolism Branch invites proposals for the establishment of additional lipid research clinics to improve the diagnosis and clinical management of lipid-transport disorders (hyperlipoproteinemias), especially those associated with increased risk of premature atherosclerosis.

Prospective applicants should send a letter of intent to NHLI as soon as possible, briefly outlining major studies to be proposed, listing key investigators, and providing estimates of the direct costs to be requested. Requests for workscopes of the proposed programs, application forms, and letters of intent should be addressed as follows:

For Arteriosclerosis SCORs, write to Dr. Gardner C. McMillan, Chief, Arteriosclerotic Disease Branch, Extramural Research and Training Programs, National Heart and Lung Institute, National Institutes of Health, Bethesda, Md. 20014.

For Pulmonary Disease SCORs, write to Dr. Claude Lenfant, Associate Director for Lung Programs, National Heart and Lung Institute, National Institutes of Health, Bethesda, Md. 20014.

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